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AN IMPROVED AUTOTRANSFUSION PRODUCT TO
CONSERVE BLOOD AND REDUCE BLOOD
REPLACEMENT NEEDS IN COMBAT

Final Report

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FOREWORD

This document is the final report for the six month feasibility research and development program for "An Improved Autotransfusion Product to Conserve Blood and Reduce Blood Replacement Needs in Combat". This feasibility program was performed by Thoratec Laboratories Corporation (Berkeley, CA) under contract number DAMD17-82-C-2084 as Phase I of the Department of Defense (DoD) Defense Small Business Advanced Technology (DESAT) Program. Under the DESAT Program, Phase I work is directed towards a six-month "feasibility-related experimental or theoretical research and development effort on a proposed idea or approach to a scientific or technical need" and is funded for up to \$50,000. Phase II of the program "is designed to allow for full-scale research and development" and is intended to be funded for up to \$500,000. Phase III of the program is expected to "include follow-on development, when necessary, or production where appropriate."

The Phase I program contract was specifically awarded by the Department of the Army (DoA) to support their program for developing new capabilities for saving lives on the battlefield and for providing needed medical support to combat units. The financial support from the DoA, and valuable discussions with DoA personnel at the Letterman Army Institute of Research (LAIR) and at the U.S. Army Bioengineering Research and Development Laboratory (USAMBRDL) at Fort Detrick are gratefully acknowledged.

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).



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SUMMARY

The enormous and uneven demands for blood during combat, the significant logistics problems of transporting and storing homologous blood, the serious potential for blood shortage, and the significant advantages of fresh autologous blood, all suggest a potentially vital role in the military for intraoperative autotransfusion. Autotransfusion can have the advantages of providing a patient with blood which is: immediately available, fresh, and his own. Additionally, autotransfusion can contribute significantly to the conservation of blood, and can save the lives of patients who might otherwise die of exsanguination due to inadequate blood supplies.

Thoratec Laboratories Corporation has been developing an improved Autotransfusion System (ATS) for use in civilian applications. As Phase I of a DESAT Program contract, Thoratec has just completed a six month feasibility study to: (1) preliminarily identify the specialized needs of the military application of autotransfusion, and the degree to which the basic Thoratec device fits those needs; (2) develop preliminary product specifications and overall system design parameters to adapt the Thoratec device to produce a specialized ATS for military use, and (3) conduct a set of in vivo tests in animals to provide an early assessment of the hematological effects of processing blood through the device.

The results of this feasibility study clearly indicate the following: There is a need for the development of a specialized ATS for the military application; the basic Thoratec ATS can provide a sound basis from which to derive a practical system for military use; and the collapsible ATS design generated during Phase I appears to address the specific needs of the military, particularly the key issue of logistics. The in vivo test results showed that the overall blood handling function of the device is convenient and efficient. Additionally, in these experiments, red blood cell damage was found to be minimal, the recovery of blood components in the salvaged blood was considered to be very good, and the relatively small changes in the measured hemostatic parameters were not very different from those observed in a control experiment.

Based upon these positive results, Thoratec believes that the continuation of this program will lead to the final goal of producing an autotransfusion system that can have a significant impact on conserving blood and saving lives under combat situations.

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I. INTRODUCTION

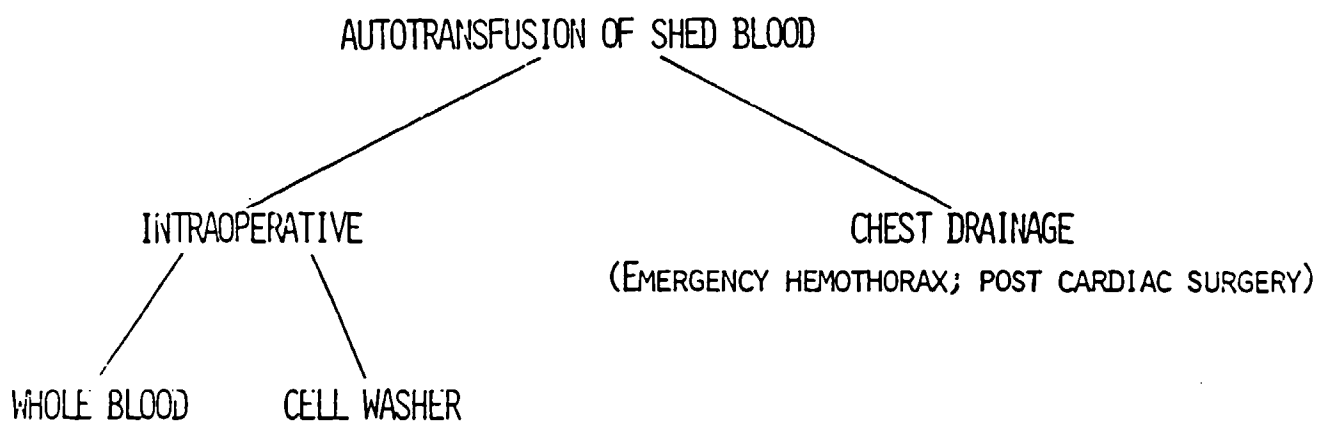
Autotransfusion is a procedure by which a patient is reinfused with his own blood. Excellent comprehensive reviews of the various types of autotransfusion have been published in recent years (Thurer and Hauer, 1982; Brizica et al., 1976), however, it is instructive to begin here with a brief overview. Autotransfusion may be classified according to the conditions under which the patient's blood is collected. (Thurer and Hauer, 1982; Emminizer, 1981). Thus, there is preoperative autotransfusion in which a patient's blood is preoperatively collected and stored to serve as an intra- or postoperative source of blood (Fleming et al., 1981; Fleming et al., 1977); intraoperative autotransfusion in which a patient's shed blood is collected intraoperatively, generally for immediate reinfusion (e.g., Noon et al., 1976; Klebanoff, 1978); and postoperative autotransfusion in which blood is collected postoperatively from mediastinal tubes placed in post-cardiac surgical patients. (Schaff et al., 1978).

Alternatively, autotransfusion may be classified into procedures in which the blood is collected electively, such as in preoperative autotransfusion, or from accumulations of shed blood, e.g., from trauma or surgical wounds. Autotransfusion of shed blood can be further classified as indicated in Figure 1. In chest drainage autotransfusion, shed blood is collected via standard chest tubes from the closed thoracic cavity under conditions of traumatic hemothorax (Davidson, 1978) or in cases of postoperative mediastinal drainage. On the other hand, intraoperative autotransfusion involves the collection of shed blood from an open cavity wound, usually from blood pools accumulating within the thoracic and abdominal cavities, during emergency or elective surgery. Furthermore, this collected blood may be returned, after filtration, directly back to the patient as whole blood ("whole blood" autotransfusion) or the collected blood may be "washed" prior to reinfusion (see below).

The focus of the present work is intraoperative whole blood autotransfusion. Reports on the intraoperative use of autotransfusion first appeared in the literature in the late 19th century, and by 1936 there were reports of hundreds of autotransfusion cases in the American medical literature. During the 1940's and 1950's, however, interest in autotransfusion waned as blood banking technology improved (Thurer and Hauer, 1982). About twenty years ago there began a resurgence of interest in autotransfusion due to a recognition of three factors: the need for means of blood conservation, inherent dangers of homologous blood transfusion, and the advantages of autotransfusion (discussed more fully below).

Intraoperative autotransfusion has been commonly used on a pre-planned basis for appropriate elective cases in which the loss of more than two units of blood may be anticipated, and in emergency cases, being particularly useful in trauma (Glover et al., 1976). The procedure has been used with generally very positive results in treating a wide range of types of cases including blunt or penetrating trauma to the chest and abdomen (Mattox et al., 1975), and in major vascular surgery (Anderson, 1975; Mattox et al., 1975; Thomas et al., 1980; Brewster et al., 1979). For example, in six years of experience with autotransfusion in major vascular surgery, Brewster et al. (1979) reported that autotransfusion provided a mean blood salvage equivalent to five units of blood per patient and the avoidance of using any bank blood in almost one-half of their elective patients, with "no significant problems... nor any morbidity or mortality

FIGURE 1



specifically related to autotransfusion". Brenner et al. (1973) reported similarly good results based upon comparisons between twenty vascular patients in whom intraoperative autotransfusion was used and twenty similar patients in whom only conventional transfusion techniques were used. Autotransfusion has been used in the emergency room as well as in the operative room, and in the smaller community hospitals (O'Riordan, 1977) as well as in the larger medical centers (Brewster et al., 1977).

Only within the last 13 years have devices for conducting intraoperative autotransfusion procedures become available. As indicated above, these commercial autotransfusion devices have been of two basic types, whole blood and cell washer. The first type is typified by those which have been marketed by Bentley Laboratories and by Sorenson Research. The Bentley device was originally developed by a surgeon in the U.S. Air Force (Kebanoff et al., 1970) and the life saving potential of autotransfusion was demonstrated with it in initial trials in Vietnam (Klebanoff, 1970). It requires approximately five minutes of set-up time and the full-time attention of a trained technician to ensure safe operation (Stehling et al., 1975). In addition to a set of disposables, the Bentley device requires a roller pump for blood collection and reinfusion, and electro-optic monitoring equipment to help minimize the risk of air embolism which was inherent in the specific device design. Despite this monitoring equipment, use of this device was associated with problems of air embolism, attributed to both operator error and design problems, and some degree of blood damage which has been attributed to the use of a roller pump for operating this system (Thurer and Hauer, 1982). Apparently because of these problems, the hardware necessary for operating this equipment has been removed from the market. The Sorenson Research Device (Noon et al., 1976; Noon, 1978) is comprised of disposable components, although certain parts are designed to be reused. The device is operated from a vacuum source (instead of a pump), requires a permanent vacuum regulator for connection to that source, and has a line which is designed to deliver anticoagulant to the blood as it is being aspirated. A major inconvenience and potential problem with this device is its somewhat involved operational procedures. Once its reservoir is sufficiently filled with blood, someone must disassemble the apparatus, use a hypodermic needle to remove air from its blood bag, hang the bagged blood and connect it up for reinfusion (generally by gravity). The blood aspirating portion of the system must then be reassembled with a new reservoir liner before suctioning of additional blood can be resumed. Thus, the use of this system, particularly its blood collecting function, must be interrupted to deliver the blood back to the patient and there are repeated requirements during each case for reassembly of the system with fresh components (Noon et al., 1976; Sorenson Research, #7510-S49). More seriously, the Sorenson intraoperative system was the subject of a recall by the Food and Drug Administration (1976) because of apparent problems in the design of its anticoagulant delivery system which mixed the anticoagulant with the blood at an uncontrolled and unpredictable rate (Thurer and Hauer, 1982). Since then, Sorenson has released a modified version of their intraoperative autotransfusion system; but it is now labeled in their recent product literature (Sorenson Research, 8/81-S2562) as "to be used with a cell washer/processor", presumably because any excessive anticoagulant will be washed away, rather than being delivered to the patient, during processing (see below).

The second type of intraoperative autotransfusion device is typified by the Haemonetics Cell Saver (Orr, 1978) and by the IBM Blood Cell Processor (IBM Corp., Purchase, NY). For the Haemonetics unit, blood is collected by vacuum aspiration, mixed with anticoagulant, and centrifuged, separating the red cells from the plasma which is then discarded. The red cells are washed with normal saline and resuspended in saline for gravity reinfusion to the patient. Cell washers are sophisticated, electromechanical

devices which are non-portable, expensive, and complicated to operate. They require a trained technician for operation and 15-20 minutes to process a volume of blood (250-500 ml). Such an interval would appear to be unacceptable in cases of rapid, life threatening bleeds (Thurer and Hauer, 1982).

The major advantages of intraoperative whole blood autotransfusion in treating hemorrhage include the following:

- The blood is immediately available for use in treating the patient. This minimizes or eliminates the delays associated with obtaining bank blood in emergency situations.
- The blood is fresh. As such, autologous blood has been reported as having relatively normal levels of 2,3-diphosphoglycerate, pH, and various clotting factors, and also as being normothermic (Emminizer et al., 1981).
- The blood is the patient's own, thus avoiding the potentially significant problems related to blood incompatibilities and other complications associated with transfusing bank blood. One of the more serious complications that is avoided with autotransfusion is the risk of hepatitis, which has been underestimated in terms of both incidence and seriousness. The transfusion of bank blood is thought to be "responsible for up to 300,000 cases of post-transfusion hepatitis and up to 15,000 cases of cirrhosis in the U.S. each year (Thurer and Hauer, 1982).
- The practice of autotransfusion can contribute significantly to the conservation of blood which, of course, is a vital and often scarce resource.
- The use of intraoperative autotransfusion can potentially save the lives of patients who would otherwise die of exsanguination due to inadequate blood supplies.

All of the above general advantages of intraoperative autotransfusion would appear to be particularly important in the treatment of combat casualties. The potential importance of autotransfusion to the military was discussed by Maj. John Rumisek in a recent article entitled "Autotransfusion of Shed Blood: An Untapped Battlefield Resource" (Rumisek, 1982). This article emphasized that the military use of autotransfusion may be particularly important for:

- easing the enormous demands on blood resources during combat situations,
- easing the significant logistics problems of providing, without delay, adequate supplies of homologous blood,
- salvaging the enormous quantities of fresh blood that are otherwise thrown away with the surgical sponges or spilled on the floor, and
- minimizing the incidence of complications associated with bank blood transfusions.

Autotransfusion may also prove to be particularly valuable for use in the medical support of the Rapid Deployment Force.

Based upon the Vietnam experience, the vital need for whole blood in the treatment of battlefield injuries is evidenced by: the use of whole blood transfusions in 16% to 46% of the hospitalized (trauma) casualties in U.S. military hospitals in Vietnam; and by the reported use of estimated averages of about 3.7 to as high as 9.0 units of whole blood per patient transfused (Mendelson, 1975). In many individual casualty cases, as much as 40 to 50 (or more) units of whole blood was transfused (Kiel, 1966; Mendelson, 1975). In general, such cases could rapidly deplete what may be an already short supply of blood. Even a short term, temporary shortage in such cases could be disastrous. One additional problem in terms of the logistics of supplying blood for battlefield casualties is, of course, the perishable nature of the product. In 1966, for example, it was reported (Kiel, 1966) that the loss of blood, largely due to outdating, was about 31%. This loss was attributed to a difficulty in forecasting the requirements for blood due to the unpredictability of the level of activity and casualties during a particular conflict.

Thus, the enormous demands for blood during combat, the significant logistics problems of transporting and storing homologous blood, the serious potential for blood shortages for battlefield casualties, and the significant advantages of fresh autologous blood, all strongly point to a valuable role for intraoperative autotransfusion if a system can be developed to meet the specific needs of the battlefield environment and conditions. As pointed out by Rumisek (1982), the evaluation of an autotransfusion system for optimal military use requires not only the consideration of the quality of the blood product produced, but of nearly equal importance is the consideration of the logistics of the transport and utilization of the autotransfusion equipment.

Thoratec Laboratories Corporation (Berkeley, CA) has been developing a new intraoperative whole blood autotransfusion system (ATS) designed for civilian applications (see Section II below). This system is believed to solve many of the basic design and operational problems experienced with earlier autotransfusion devices as discussed above. Thoratec believes that this basic system is also particularly suited for adaptation, through system design modification, to also fulfill the specific needs of the military. As such, with the support of the Department of the Army (DoA), Thoratec carried out a six month feasibility study (Phase I DESAT program) in which the following work was accomplished:

- (1) the specific requirements of the DoA for autotransfusion were preliminarily identified through early discussions with DoA personnel;
- (2) a preliminary set of product specifications and an overall system design was generated so as to meet the requirements of the DoA, with particular consideration given to the logistics of autotransfusion;
- (3) a prototype model of a Thoratec DoA-ATS based upon tasks 1 and 2 above was fabricated, and shown to and discussed with DoA personnel; and
- (4) a preliminary series of in vivo tests in animals was conducted with the then current, basic Thoratec ATS prototype.

The results of the Phase I program were very positive in that the basic prototype Thoratec ATS appears to have design and performance characteristics particularly suited for the military application and it can be readily adapted to address the important logistics issues.

The remainder of this document begins with a brief general description of the basic Thoratec ATS, and then continues with discussions of the results from Phase I tasks 1-4 (above).

II. THE BASIC THORATEC AUTOTRANSFUSION SYSTEM

The basic Thoratec Autotransfusion System (ATS) is designed to be used for the intraoperative salvage of whole blood from a cavity (generally thoracic or abdominal) wound during elective or emergency-trauma surgery. The function of the Thoratec ATS device includes blood collection with the automatically metered addition of an anticoagulant solution, blood defoaming and initial gross filtration, temporary blood storage, and elective blood reinfusion with final micro-filtration. The system has been designed to achieve the objectives of safety, performance, and ease of use.

The features of this new system appear to represent major advances over previous whole blood intraoperative autotransfusion devices, in that a low cost, simple-to-operate system provides controlled reinfusion of shed blood, without interrupting blood suction or requiring replacement parts and reassembly of the device after autotransfusion of each unit of blood. Furthermore, the process of anticoagulant mixing with the blood is more effectively accomplished than has previously been possible. The result is a device which provides the ability to rapidly salvage and reinfuse blood in cases of intraoperative blood loss. This basic Thoratec ATS forms the "backbone" for the Thoratec DoA (Department of the Army) ATS being developed under the present DESAT program.

III. PHASE I PRELIMINARY IDENTIFICATION OF THE MILITARY REQUIREMENTS FOR AUTOTRANSFUSION (MEETINGS WITH DEPARTMENT OF THE ARMY PERSONNEL)

A key objective of Phase I of our Department of the Army autotransfusion system (TLC DoA-ATS) contract program was considered to be the preliminary identification of the special requirements that the DoA has for using autotransfusion for the resuscitation of combat casualties. Broadly speaking, it was hoped that the early identification of these requirements would help to insure that the ATS device developed by Thoratec will have the greatest likelihood of fulfilling the specialized needs of the Army. With respect to the Phase I program, these results were expected to provide direction for: (1) initiating our preliminary overall system design (see Section IV), and (2) evaluating the overall feasibility of the proposed ATS design. Toward these ends, we requested that meetings be arranged with appropriate DoA medical and bioengineering personnel for discussions on autotransfusion technology and logistics.

DoD WORKSHOP ON AUTOTRANSFUSION

Three Thoratec personnel attended the DOD "Workshop on Autotransfusion" at the Annual Meeting of the Society of Armed Forces Medical Laboratory Sciences (March 25, 1982 in Reno). The workshop included extensive lectures by Jerome Hauer (Beth Israel Hospital, Boston) and by Dr. Robert Thurer (also from Beth Israel). They presented an overview of autotransfusion and overall general discussions as to the applicability of various types of autotransfusion for use by the military. Briefly, they discussed the problems encountered with transfusions of banked blood, particularly the significant risks of hepatitis which were thought to be generally underestimated. The potential significant advantages of autotransfusion were discussed as well as its potential problems and contraindications. There was a discussion of whole blood autotransfusion system devices which are, or have recently been, available commercially and the significant problems which have been encountered. With respect to the military application of autotransfusion, the logistics problems of transporting and making sufficient quantities of homologous blood available to combat casualty victims were discussed, along with the apparent logistics priorities of transporting military material which is "bullets, beans and blood", in that order. It was suggested that intraoperative autotransfusion would be particularly valuable for resuscitation of combat casualty cases in which the rapid infusion of blood in amounts approaching or exceeding replacement of the recipient's total blood volume was necessary. Such cases could easily deplete valuable, and perhaps already scarce, stores of homologous blood.

MEETINGS OF TLC PERSONNEL WITH DoA MEDICAL PERSONNEL AT LAIR

At Thoratec's request, a meeting at the Letterman Army Institute of Research (LAIR) was arranged between six Thoratec personnel and several DoA medical personnel at LAIR. It was understood that the meeting was to be an informal discussion and exchange of ideas. Following our prepared outline, the discussion initially centered on intraoperative whole blood autotransfusion in general and the specific requirements that the Army has for a practical intraoperative autotransfusion system (ATS). The mechanical operation of an early prototype of the Thoratec ATS was then demonstrated. Finally, we discussed specific observations on the design and function of the Thoratec ATS device and recommendations for further development. Key issues discussed at the meeting are briefly summarized below.

General Concepts in the Potential Military Use of Autotransfusion: In general, the discussants stressed that an intraoperative ATS unit can only be used as close to the site of the actual battlefield injury as there are qualified surgeons having the expertise to use the specific device. In conventional combat situations, this means that such devices would be used in "MASH units", in which emergency surgery aimed at stabilizing the patient is performed, and in "theatre hospitals", one step further from the front, in which definitive secondary procedures are carried out. However, it was thought that an intraoperative ATS would not be used at the level of the "battalion aid stations", the first echelon of care close to the front, which provides (at most) only relatively "primitive" care. When asked whether the Thoratec ATS-type device would be used in rescue helicopters, it was stated that it is "almost impossible to do anything in a helicopter" and that even setting up an IV is difficult under such conditions.

We discussed the possible use of the Thoratec DoA-ATS for the medical support of the Rapid Deployment Force (RDF) which is designed to include small, self-sufficient combat units. One key specific problem is clearly that of the logistical difficulties in carrying and storing blood for these highly mobile units. Therefore, the development of a transportable, easy to operate ATS device was considered to be potentially very valuable for the medical support of the RDF.

The Basic Thoratec Prototype ATS Device: Based upon the bench demonstration of the TLC prototype ATS, it was felt that the device would have quite favorable performance characteristics for the Army application if it performs similarly in actual practice. Specifically, the speed and convenience with which blood can be handled by the system was considered to be very good, and the system was considered to be relatively easy to use. A five foot length for the blood suction line (including the suction handle) was considered to be quite adequate, although, if possible, a longer line would be more convenient. The use of a blood micro-filter in the blood delivery line to the patient (as included in the prototype Thoratec ATS) was considered to be essential.

Based upon the size and shape of the prototype version of the Thoratec ATS which was demonstrated, there was some concern that too much space may be required for packaging the device and, as a disposable device, it was felt that shipping and storing a large number of these devices may have the potential for presenting its own logistics problems. Thus, it was repeatedly emphasized that, to avoid such problems, a key requirement for practical use of autotransfusion by the Army is that the ATS device be designed to be extremely transportable and easily stored, i.e., lightweight, as small in size as possible, and rugged. In response to this discussion, Thoratec has subsequently

addressed this issue and substantially reduced the potential of the transportability and storage considerations becoming a problem through a modification of the Thoratec ATS system design (see Section IV below). The key importance of the "logistics of transport and utilization of autotransfusion equipment" to the military situation has also recently been emphasized in the literature (Rumisek, 1982). Because cell-washer-type ATSs are not easily transportable, are relatively fragile, require close user attention, and require a relatively high level of user expertise, it was generally thought that such devices would find use only in surgical suites relatively far removed from the battlefield.

An additional discussion question referred to the present packaging of the anticoagulant solution in glass bottles. It was mentioned that Thoratec has plans to look into the possible use of plastic containers as a replacement for the glass. The potential advantages and disadvantages of packaging the ATS with anticoagulant containers having only the dry anticoagulant chemicals which would be reconstituted in the field was also discussed.

The discussants also emphasized that the device must be as self-contained as possible for its operation. In this respect, it was stated that even the availability of an IV pole, which will be needed for mounting the Thoratec DoA-ATS device, cannot be counted on since IV bottles are often hung from the ceiling (eliminating IV poles) and, even if IV poles are used, they may not be available for the ATS. It was concluded that we must, therefore, make provision for incorporating some type of support pole for the device. However, at the same time, there was a concern over the problem of excessive shipping weight, size, and cost for IV-type poles. Thoratec has subsequently addressed this problem and a solution has been found (see Section IV below).

The discussants felt that an appropriate vacuum source will be available in the environment in which the device is expected to be used. Therefore, Thoratec's development of a portable vacuum pump operated from a rechargeable battery would not be investigated. (Note, however, that a subsequent discussion suggests that the investigation of alternative vacuum sources should be reconsidered).

The Thoratec DoA-ATS will be used for blood salvage from a cavity, particularly as related to thoracic and abdominal injuries. The device itself will probably not be mounted directly on the operating table, but should be mounted on an IV-type pole near the table and within easy reach of the anesthetist. The anesthetist will most likely be responsible for the operation of the ATS device.

Additional Discussion: With respect to more general aspects of autotransfusion, a discussion was initiated concerning the potential for problems associated with general blood contamination, particularly in cases of massive autotransfusion. The contamination referred to includes that associated with infection, tissue debris, and damaged blood components. The potential problems referred to include infection, embolism, and coagulopathies. On the other hand, however, without minimizing the importance of these potential problems, it was quite strongly stated that, despite the potential risks, massive autotransfusion can be a means for saving the lives of wounded individuals who might otherwise exsanguinate due to inadequate blood supplies. The military scenarios of battle conditions in which bank blood will either not be available, or be an extremely scarce resource was discussed and the value of autotransfusion under these potentially very real conditions recognized. Furthermore, the use of antibiotics and blood micro-filtration should help to alleviate at least some of these potential problems. The philosophy is to first save the patient's life with blood reinfusion, and then treat any infection. The literature concerning these issues has recently been reviewed in detail by Thurer and Hauer (1982).

It was felt that the Thoratec ATS prototype's aspiration flow capacity for an intraoperative ATS device should be quite sufficient. Ideally, the collected blood should be available for reinfusion with minimum delay and at as high a flow rate as possible. It was felt that the Thoratec ATS would have good overall blood handling and blood reinfusion characteristics. In contrast, it was commented that, for "massive bleeds", cell washer-type ATS devices may be inappropriate because they are too slow, i.e., too much time is required for processing the blood.

MEETING OF THORATEC PERSONNEL WITH DoA PERSONNEL AT USAMBRDL

Based upon the recommendation of personnel at LAIR, and with the approval of the program's Contracting Officer's Representative, Thoratec arranged for a meeting with DoA personnel at the United States Army Bioengineering Research and Development Laboratory (USAMBRDL) at Fort Detrick, Maryland. The overall objective of this meeting was to familiarize the USAMBRDL personnel with the Thoratec ATS device and development program, and to obtain their input. The presentation at Fort Detrick included: (1) a brief general description of intraoperative autotransfusion and a discussion of the potential value of intraoperative autotransfusion to the Army, (2) a description and bench demonstration of an early prototype version of the Thoratec ATS, (3) a discussion of the results of our earlier ATS "discussion group" meeting with Army medical personnel at LAIR (see above), (4) a discussion and presentation of the overall preliminary system design concept direction which was based upon the results of our meeting at LAIR, and (5) a demonstration and discussion of our newly developed, self-contained, collapsible ATS and IV-type pole (see Section IV below). The comments on the collapsible ATS were positive and it was felt that the preliminary system design appeared to be properly addressing potential problems associated with the logistics of autotransfusion, which is clearly a key consideration in the successful development of an ATS for military use. Additionally, the meeting participants suggested that the collapsible IV pole, designed as part of the collapsible Thoratec DoA ATS and fabricated for our prototype, might be presented to the military as a product in its own right since it appears that it may have advantages over that which is presently available.

THORATEC PRESENTATION AT FORT DETRICK

Thoratec had a second opportunity to meet with DoA personnel at Fort Detrick on October 5, 1982. At this meeting Thoratec gave a presentation of the material covered in this document, i.e., the results of Thoratec's Phase I program. A valuable discussion on the subject of autotransfusion ensued.

IV. PHASE I PRELIMINARY DoA ATS SPECIFICATIONS AND OVERALL SYSTEM DESIGN

Based upon our discussions with DoA medical personnel at LAIR, preliminary ATS specifications were written, a preliminary overall system design concept was developed, and a system prototype was designed and fabricated to demonstrate the system design concept. These were derived by appropriate modifications of the basic Thoratec ATS which is the "backbone" of the system. The product specifications and system design developed under this Phase I feasibility program are briefly summarized below. They are preliminary and it is expected that they will be further detailed and refined.

PRELIMINARY PRODUCT SPECIFICATIONS FOR THE THORATEC DoA-ATS

1.0 DESIGN OBJECTIVE

The Thoratec Department of the Army-Autotransfusion System (DoA-ATS) is to be designed for intraoperative salvage of shed blood from an open wound. The device will: collect the blood with appropriate anticoagulant addition, filter the blood, and facilitate its rapid return to the patient. The Thoratec DoA-ATS will be self contained, requiring only a suitable source of vacuum and it will be highly transportable, i.e., packaged as a lightweight and relatively small package. The device will be completely disposable with no hardware components required. It will be designed for rapid set-up and ease of use.

2.0 SYSTEM CHARACTERISTICS

2.1 Functional Performance

- | | |
|--|--|
| - Aspiration blood flow rate capacity: | 600 to 800 ml/min |
| - Total System Blood volume holding capacity: | 3000 ml |
| - Total salvaged blood flow-through capacity per device: | 20 liters (minimum) |
| - Blood/CPD mixing ratio: | maintained between 5 to 1 and 10 to 1 to provide an activated clotting time of greater than 480 sec. |

- Two stage blood filtration provided:

first stage filters
blood upon aspiration
second stage
filters blood
upon reinfusion

2.2 Product Use

The DoA-ATS will be a single-use, completely disposable device.

2.3 General Physical Description

The Thoratec DoA-ATS will be comprised of a collapsible blood reservoir with tubing connections to a hand-held suction wand for aspirating from an accumulating pool of shed blood. The device will include an integral anticoagulant delivery system for automatically mixing anticoagulant with the blood as it is being aspirated by the wand. The system will also include a special integral blood delivery system and patient reinfusion line. The reinfusion line includes an in-line blood microfilter which will be a readily replaceable system component. The packaged system will include a lightweight, collapsed, readily expanded pole (with integral collapsible base) to serve as an "IV pole" support for the system. Anticoagulant solution will be provided in 500 ml glass containers.*

2.4 Packaging and Accessories

The device will be supplied in a sterile double-wrapped package. This will help to ensure the maintenance of sterility during the set up procedure and will allow the user to set up the system some time in advance, in anticipation of the arrival of casualties, without compromising sterility. The sterile system package will be protected for shipping and storage by the use of individual cardboard cartons which, in turn, will be boxed as six cartons (or systems) per cardboard shipping case. The collapsed IV-type pole and anticoagulant bottle can be provided within each individual system carton or grouped within shipping cases. Additional accessories for the Thoratec DoA-ATS will include replacement containers of anticoagulant.

2.5 Biological Interface

As a minimum requirement, the device will be tested for blood interaction according to in vitro/ex vivo blood testing protocols described in the recently published AAMI/ANSI Standard for Autotransfusion Devices (Hauer and Orr, 1982). Accordingly, the system components will be tested for their biocompatibility and pyrogenicity. The device will be ethylene oxide sterilized.

* The question of the need for a design replacement for the glass container should also be addressed .

3.0 POTENTIAL ADDITIONAL CHARACTERISTICS

- Portable vacuum pump operated from rechargeable batteries.
- Plastic rather than glass containers for the anticoagulant.

4.0 SPECIFIC QUALIFICATION TESTS REQUIRED

4.1 Physical Tests

- Testing according to the AAMI/ANSI Standard for Autotransfusion Devices (Hauer and Orr, 1982), including:
 - freedom from particulate contamination
 - system integrity tests
 - testing for proper blood/CPD ratios
- Appropriate military specifications

4.2 Biological Tests

- AAMI/ANSI Standard
- Blood cell/system interaction (*ex vivo* blood damage tests)
- Toxicity: USP Class VI required for blood contacting surfaces.
- Sterility: USP procedures to be followed.
- Pyrogen: According to the USP rabbit tests or the Limulus Amoebacyte Lysate test.

PRELIMINARY OVERALL SYSTEM DESIGN AND PROTOTYPE FABRICATION

During Phase I, an overall system design concept was developed to incorporate the Army's special requirements into the basic design of Thoratec's prototype ATS. Special features of this completely self-contained system design, include: a collapsible blood reservoir which is readily expanded to a 2.5 liter blood container capable of withstanding the required suction vacuum level; and a specially designed collapsible IV-type pole which is easily set up, capable of supporting the fully loaded system, and fabricated out of lightweight, inexpensive materials. With the components packaged in their collapsed configuration, the Thoratec DoA-ATS can be provided as a system which is: relatively small and lightweight for facilitating shipping and storage; easily set up and operated; and completely self-contained as a disposable device, requiring no hardware, only an appropriate source of vacuum for its operation.

Three versions of the collapsible blood reservoir concept were developed in at least preliminary form, and an early prototype of one of these has been fabricated. The collapsible IV pole design works so that, with a minimum of manipulation, the pole and its integral base can be correctly and completely assembled from its collapsed configuration in a matter of only seconds.

To provide a means of demonstrating the system design concept, a complete prototype system model was constructed. This model included the collapsible blood reservoir, collapsible IV-type pole, and the associated brackets and fittings. It was used to facilitate discussions in meetings with DoA medical and bioengineering personnel to help evaluate and further develop the preliminary system design. Two such meetings at Fort Detrick have been held to date (June 18 and October 5, see Section III above).

V. PHASE I IN VIVO TESTS OF THE PROTOTYPE THORATEC AUTOTRANSFUSION SYSTEM

The prototype Thoratec ATS (Autotransfusion System) was tested in a preliminary series of in vivo experiments in dogs at Thoratec's Surgical Facility. The protocol was designed so that the function of the prototype ATS could be observed during in vivo use and so that the hematological effects of processing blood through the ATS could be preliminarily assessed.

A total of eight experiments were conducted during this Phase I program. These eight animals were divided into two test groups, the "ATS group" and the "control group". In the ATS group, the prototype ATS was tested under specified surgical conditions in six animals. Two animals were used for testing in the control group. The control animals were subjected to the same surgical conditions, however, blood was collected in standard commercial blood bags, rather than with the ATS, and then delivered back to the animal through a standard commercial blood delivery set.

METHODS

ATS Prototype Preparation: For each experiment, a prototype ATS unit was assembled and set up for use on an IV pole. In place of the standard CPD (anticoagulant citrate, phosphate, dextrose, U.S.P.) bottle used with the ATS, a specially designed CPD-bottle-substitute was constructed from a graduated cylinder and used with the test ATS. This allowed accurate measurements of the volumes of CPD used by the ATS during the tests.

Experimental Animal: Eight random source, healthy dogs, weighing 28-56 kg were used. Animals were purchased from a licensed dealer in central California.

Physical Examination: The animal arrived at the Thoratec Surgical Laboratory on the morning of the experiment. Upon arrival, each animal was weighed and given a physical examination. Obvious signs of illness were considered justification for exclusion from the study.

Housing: During the pre and post surgical periods, dogs were housed in individual pens. The size of each pen was in accordance with the recommendations given in The Guide to the Care and Use of Laboratory Animals, DHEW Publication No. 80-23, 1980. Food and water were available at all times during the post operative period. Pens were bedded with saw and were completely cleaned and disinfected daily. The air temperature of the animal pens was maintained at a minimum of 62°F with 20 air changes per hour.

Anesthesia and Pre-Surgical Preparation: As a preanesthetic, Atropine (0.02 mg/lb body weight) was administered subcutaneously thirty minutes prior to anesthetization with Thiamylal Na (5 mg per lb body weight). When the animal was sufficiently relaxed, endotracheal intubation was accomplished using direct vision. Anesthesia was maintained with halothane (1.5-2.5%) delivered via positive pressure ventilation (Searle Adult Volume Ventilator) using appropriate ventilator settings. The breathing gas included 30% O₂. The animal was placed in dorsal recumbency on a warm water

blanket. EKG leads were placed for continuous recording of the EKG and for heart rate measurement.

Surgical Procedure and Baseline Hematologic Evaluation: The left femoral artery was isolated and catheterized using a commercially available 14 ga. Teflon catheter. This catheter served as the site for continuous recording of the arterial blood pressure and for obtaining arterial blood samples for blood gas analysis. The left femoral vein was isolated and catheterized to provide a site for obtaining blood samples from the animal.

The right external jugular vein was isolated in the neck. A "pocket" to pool blood was developed within the surrounding tissue and maintained with retractors. A 14 ga. Teflon catheter was inserted into the jugular vein so that it was directed towards the heart. This served as the blood infusion site. Distal to this venous catheter, the jugular vein was incised so that it also served as the bleeding site. Bleeding from this incision into the tissue pocket was controlled via a vascular clamp.

At this time, a blood sample was obtained from the animal and analyzed as described below. This blood sample served to provide baseline, or pre-autotransfusion, hematological data. Additionally, an arterial blood sample was obtained for baseline blood gas analysis.

Autotransfusion Procedure: The autotransfusion procedure used with the ATS group animals is outlined in Figure 2. In each experiment at least twelve autotransfusion cycles were conducted. Each cycle consisted of the sequence of bleeding, blood collection with the ATS, and blood delivery back into the animal. The system was generally operated with an attempt to maintain the suction tip below the surface of the blood pool with the aspiration conducted in a continuous manner. In most instances, however, the blood aspiration procedure was more intermittent than continuous because the blood aspiration flow rate of the ATS was generally greater than the flow rate of bleeding from the wound. In addition, in certain instances, blood was also purposely aspirated with the suction tip held at the blood/air interface so that the system function could also be observed under such conditions. In each cycle, blood was aspirated as it was bled from the jugular vein until approximately 10% of the total blood volume (estimated as 85 ml/kg body weight) had been bled and aspirated. CPD was automatically mixed with the blood as it was aspirated by the ATS. The anticoagulated blood (blood + CPD) was allowed to accumulate in the ATS to estimate the volume of collected blood before reinfusion. The volume of CPD delivered to the collected blood was measured using the calibrated scale on the CPD container and the blood: CPD volume ratio (R) was calculated. Blood was reinfused as soon as possible. The blood reinfusion line integral to the prototype Thoratec ATS includes an in-line blood microfilter. Blood samples (the "ATS samples") were obtained from the ATS as the blood was reinfused into the animal. A minimum of ten minutes was allowed to elapse between the completion of infusion and the start of collection of the next blood volume. Blood samples (the "dog samples") from the animal were obtained via the femoral vein catheter just prior to the beginning of the next bleeding/collection episode.

Only as required during the experiment, 1.0 gm doses of calcium gluconate were administered intravenously. The decision to give calcium was determined during the experiment according to the condition of the animal as judged by the arterial blood pressure and EKG.

Figure 2: ATS AND SHAM ATS EXPERIMENTAL FLOWSHEET

Prepare "ATS" prototype and animal.



Obtain baseline blood samples from dog.
Record HR and BP.



Bleed animal and aspirate blood. Record
aspirated blood and CPD volumes.



Obtain blood sample from ATS circuit.
Record HR and BP.



Infuse recovered blood.



Obtain blood sample from dog.
Record HR and BP.



Wait one day.



Obtain blood sample from dog.



Sacrifice. Perform necropsy and
retain tissue samples as appropriate
for pathology examination.

[Repeat the procedure
so as to complete a
minimum of 12 cycles
of autotransfusion.

On the day following the procedure, a final blood sample was drawn and euthanasia was accomplished using an overdose of sodium pentobarbital.

Control Experimental Procedure: In two control experiments, the animal was anesthetized and prepared according to the surgical procedure given for the ATS group animals. Additionally, in one of the control experiments (animal A5) a cannula was placed in the jugular vein distal to the vascular clamp. In place of bleeding and collection of the blood with the ATS, blood volumes were collected via this distal jugular vein cannula into a commercial blood collection bag (Cutter Laboratories, Berkeley, CA) containing an appropriate volume of CPD (i.e., to provide a blood:CPD volume ratio of 7:1). In the second control experiment (animal A7), the animal was bled from the jugular vein into the tissue pocket (as for the actual ATS test) and the blood was simply siphoned from the wound into the commercial CPD-containing blood collection bag. In both experiments, the animal was bled into the blood bag until approximately 10% of the animal's total blood volume had been collected. The blood volumes collected in the bag were measured by weighing. The salvaged blood was reinfused from the blood bag through a standard blood micro-filter (Model 201) Swank Blood Transfusion Microfilter, Pioneer Viggo, Beaverton, OR) and intravenous blood delivery set (Model 814-30 Blood Set, Cutter Laboratories, Berkeley, CA) into the proximal jugular vein catheter. Blood samples were obtained from the infusion line during reinfusion and these were analogous to the "ATS blood samples". A minimum of ten minutes was allowed to elapse between completion of infusion and the start of collection of the next blood volume. Blood samples from the animal were collected via the femoral vein catheter just prior to the beginning of the next collection episode and these were analogous to the "dog blood samples". A total of twelve bleeding/reinfusion cycles were conducted using a new blood bag each time. Blood samples were obtained and tested as for the actual ATS test. On the day following this sham ATS procedure, a final blood sample was obtained from the animal, and euthanasia was accomplished using an overdose of sodium pentobarbital. Thus, the control group experiments were carried out in a manner analogous to the ATS group experiments as outlined in Figure 2.

Blood Testing: As indicated above, in both the ATS and control group animals, a baseline blood sample was obtained from the animal prior to the ATS (or sham ATS) procedure. "ATS" blood samples from the collected blood-CPD volumes were obtained from the ATS blood reinfusion line (or from the standard blood delivery line in the case of the controls) after each blood collection, during blood delivery to the animal. Also, blood samples were obtained from all animals ten minutes after the completion of the reinfusion of each of the blood-CPD volumes. A blood sample was also taken from each animal on the day following the procedure, just prior to sacrifice.

As indicated in the schedule given in Figure 3, blood samples were tested to measure one or more of the following: activated clotting times (ACT), plasma hemoglobin concentration, hematocrit, hemoglobin, white cell counts, platelet counts, fibrinogen, calcium, and arterial blood gases. The measurement techniques were according to procedures standard for the Thoratec Surgical Laboratory, as briefly summarized below. Blood hematocrit was measured using centrifugation of blood collected in micro-hematocrit tubes in the usual manner. Plasma hemoglobin levels were measured by near-ultraviolet spectrophotometry according to the methods described by Harboe (1959). Activated clotting times were measured by a Hemochron (Model 400, International Technidyne Corp., Metuchen, NJ) using standard blood coagulation test tubes (CA510 Celite Activated, Hemochron). White blood cell counts were measured by Coulter counter (Model 10; Coulter Electronics, Inc., Hialeah, FL). Platelet counts were measured by phase microscopy according to Brecher et al. (1953). Plasma fibrinogen levels were measured using a modification of the Ratnoff-Menzie

Figure 3: BLOOD SAMPLE & PARAMETER MEASUREMENT SCHEDULE
FOR ATS AND CONTROL GROUP EXPERIMENTS

MEASURED PARAMETER	Cycle #													
	Baseline Dog	1 ATS DOG	2 ATS DOG	3 ATS DOG	4 ATS DOG	5 ATS DOG	6 ATS DOG	7 ATS DOG	8 ATS DOG	9 ATS DOG	10 ATS DOG	11 ATS DOG	12 ATS DOG	1-day post Dog
ACT	x	x	x	x	x	x	x	x	x	x	x	x	x	x
H-crit	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Hb	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Platelet count	x	x		x		x	x			x	x		x	x
WBC count	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Plasma Hb	x	x			x	x				x		x	x	x
Ca	x	x				x				x			x	x
Albumin	x	x				x				x			x	x
Fibrinogen	x	x				x				x			x	x
Blood gases	x					x				x			x	x

NOTES:

The cycle numbers refer to successive episodes of bleeding, blood collection and reinfusion.

"ATS" indicates that the sample is obtained from the ATS device just prior to reinfusion.

"DOG" indicates that the sample is obtained from the animal ten minutes after blood reinfusion.

The schedule of parameter measurements was simply extended when more than 12 cycles were carried out.

method according to Lerner et al. (1968). The presence of fibrin monomer and/or fibrin split products was screened using the plasma protamine paracoagulation test method described by Kidder et al. (1972). Blood smears were prepared and stained for microscopic examination. Total calcium levels were determined at a commercial clinical veterinary laboratory using their automated equipment. Arterial blood gas levels were measured (at 37°C) using standard blood gas analysis techniques (Model 1303 Blood Gas Analyzer, Instrumentation Laboratories, Lexington, MA).

Post ATS Procedure: At the conclusion of the ATS (or sham ATS) procedure, the catheters were removed from the animal, his surgical wounds were closed, and the animal was allowed to recover. The major components of the prototype Thoratec ATS were opened and examined for the presence of thrombus.

On the day following the procedure, the animal's condition was observed and noted and a blood sample from the animal was obtained. The animal was then deeply reanesthetized with sodium pentobarbital, exsanguinated, and subjected to a necropsy examination (P. Litwak, D.V.M, Ph.D.). Catheterization sites and the jugular vein blood collection pocket were examined. The pleural cavity, lungs, heart, kidneys, spleen, liver and gastrointestinal tract were all examined. Multiple samples from the lung, and from other of these tissues, were taken and fixed in 10% formalin. These tissue samples were subsequently examined microscopically by a licensed veterinary pathologist (Veterinary Reference Laboratory, San Leandro, CA).

Experiment Numbers: Note that our animal experiments are identified by a consecutive numbering system. The experiments conducted for this program begin with animal A4 and run through animal A12, except for animal A8 who was rejected from the study because of obvious signs of illness prior to the study. Experiments A1-A3 were conducted prior to the awarding of this contract.

DATA ACQUISITION AND ANALYSIS

The EKG and arterial blood pressure were monitored continuously. The heart rate was determined from the EKG record. Particular attention was given to noting their levels and variation with bleeding, blood-CPD infusion, and also during calcium gluconate infusion if administered.

The measured ACT for the blood obtained from the ATS circuit and the measured mixing ratio of blood to CPD were used to provide an assessment of the adequacy of the CPD-blood mixing function. According to the recently proposed AAMI/ANSI Standard for Autotransfusion Devices (Hauer and Orr, 1982), an ACT of greater than 480 seconds is desirable for aspirated blood flowing through the ATS circuit.

The measured values of plasma hemoglobin, hematocrit, white cell counts, platelet counts, fibrinogen and ACT were plotted as a function of time and also against the autotransfusion cycle number to provide an indication of the effects of the Thoratec ATS autotransfusion process on the blood. As appropriate, corrections for blood dilution by CPD were made.

RESULTS

A total of eight *in vivo* tests were conducted. These included six animals (dogs) in which the ATS was tested (the "ATS group" animals) and two animals which served as controls. In each of the ATS group experiments, a total of approximately 100% to 200% of the animal's total blood volume (equivalent to 3.4 to 5.3 liters of blood) was autotransfused (Figure 4). These totals were comprised of 12 to 16 successive autotransfusion cycles, each of which included: bleeding into the surgical wound pocket, blood collection with CPD (anticoagulant) addition to the blood by the ATS, temporary blood storage, and intravenous blood reinfusion from the ATS through a blood microfilter into the animal. The average volumes of blood autotransfused per ATS cycle (over the first 12 cycles) ranged from about 8.1 to 11.5% of the animal's estimated total blood volume (Figure 4).

In the control group experiments, blood was collected into commercial blood bags containing CPD, rather than by aspiration with the ATS, and then delivered back to the animal through a standard blood micro-filter and intravenous blood delivery set. In each of the two control experiments, a total of 110% of the animal's estimated blood volume was processed (Figure 4). These totals were comprised of 12 successive sham autotransfusion cycles with each cycle handling 8.4 to 9.6% of the animal's total estimated blood volume.

Hematologic Assessment: Table I gives the values of the seven hematologic parameters measured from animal blood samples taken under baseline (pre-autotransfusion) conditions for the two control and six ATS group animals. Figures 5A, B and C give plots of the hematocrit, plasma hemoglobin levels, platelet counts, white blood cell (WBC) counts, activated clotting times (ACT), and fibrinogen levels for the two control group animals. In all graphs, the parameter values are plotted against the autotransfusion cycle number, with the baseline (B) and "24-hour" post-procedure (P) values appropriately included. All parameter values are plotted as a percent of the animal's baseline value, except for the plasma hemoglobin values which are plotted in absolute units. In all cases, the data points marked by the "circles" and connected with lines indicate measurements from blood sampled from the animal, while the data points marked by the "squares" indicate measurements from the collected ATS (or sham ATS) blood-CPD mixtures. Since there were only two control experiments, the "circle" and "square" symbols indicate the average value between the two experiments and the "error bars" indicate the range of the values from the two experiments. Note that the measured parameter values for the blood sampled from the collected blood-CPD mixture in the blood bag ("squares") are altered not only by the bleeding and blood collection process, but also by the simple dilutional effect of mixing the CPD with the collected blood. Knowing the measured value of the blood:CPD volume ratio, R, this dilutional effect was corrected for by simple calculation and the resulting corrected ATS sample parameter values are indicated by the "triangles" (the error bars for these symbols were left out for clarity).

Figures 6A, B and C present the same hematologic data for the pooled ATS group experiments. In this case, however, the "circle" and "square" symbols and error bars indicate the mean values \pm SEM (the standard error of the mean) for the six ATS group experiments. Also, as for the control group plots, the parameter values for the samples from the ATS collected blood-CPD mixtures were plotted directly ("squares") and as corrected by calculation for the simple dilutional effect of CPD addition ("triangles"). Note that for the pooled ATS group, data for only the first 12 autotransfusion cycles of the experiment are plotted since only in four of the six experiments were more than 12 cycles conducted (e.g., 13 cycles in animals 6 and 12, and 16 cycles in animals 9 and 11).

Figure 4: BLOOD VOLUMES AUTOTRANSFUSED PER CYCLE

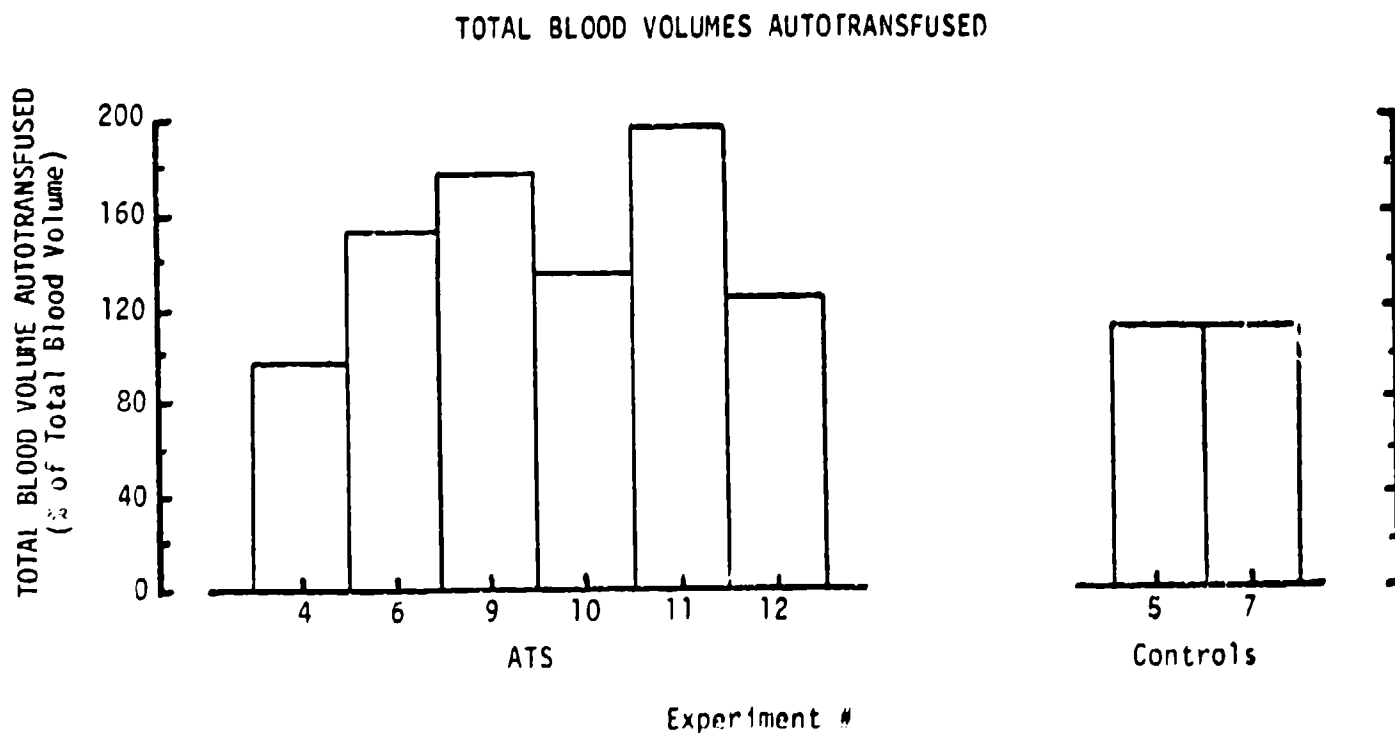
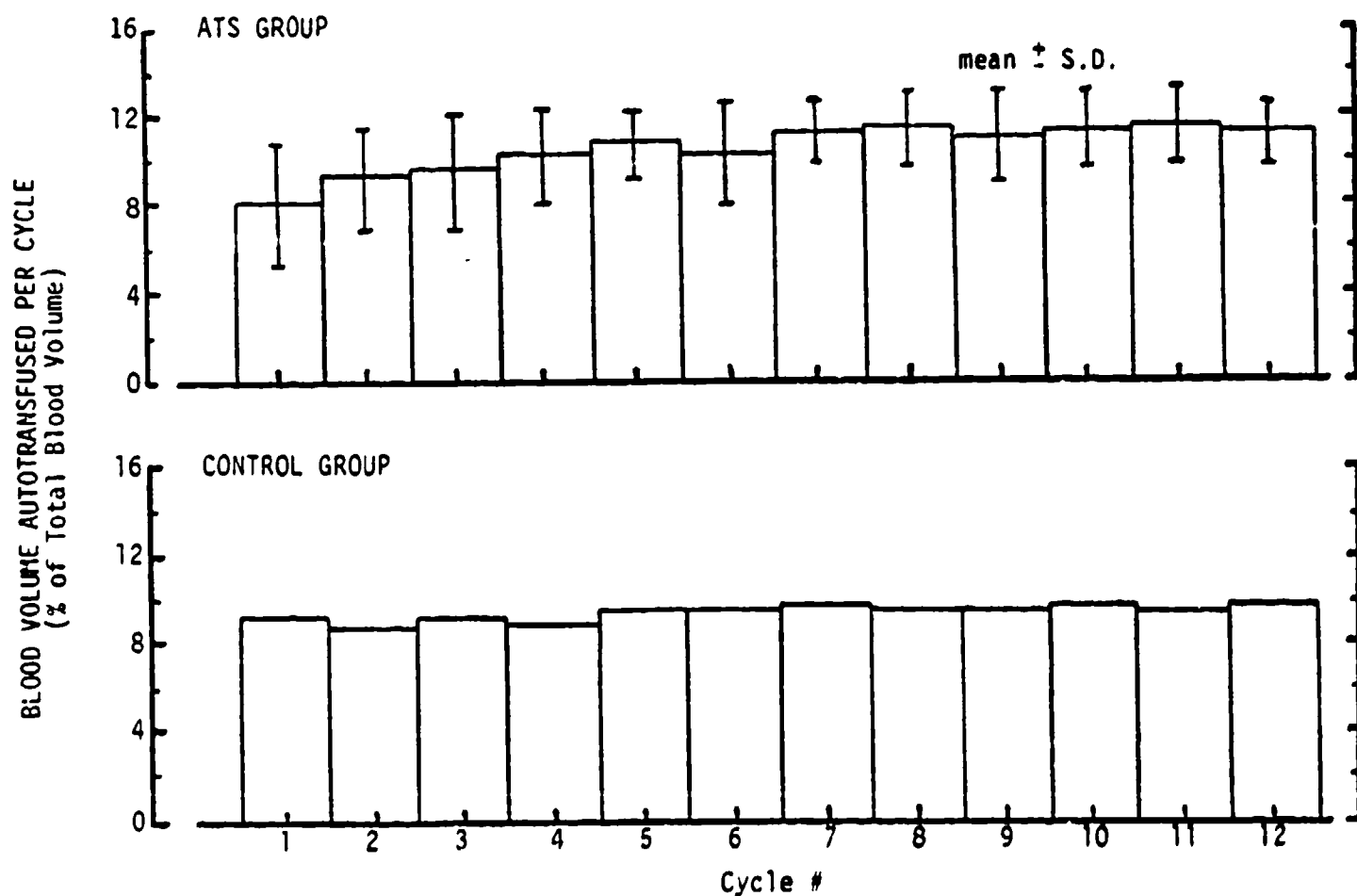


TABLE I

BASELINE BLOOD PARAMETER VALUES

	Animal No.	Hematocrit	Hemoglobin (g%)	Plasma		Platelets (X10+5)	WBC (X10+3)	Fibrinogen (mg/dl)	ACT (sec)
				Hemoglobin (mg/dl)					
C O N T R O L	A5	41.0	14.4	8.5		280	16.8	403	99
	A7	35.0	12.0	4.0		325	14.9	362	92
	Group Average	38.0	13.2	6.3		303	15.9	383	96
A T T R E S S E D G R O U P	A4	37.0	13.4	2.0		393	11.6	228	76
	A6	33.5	12.0	2.0		343	11.0	308	94
	A9	44.0	15.6	3.0		273	11.7	388	117
	A10	41.5	14.9	4.3		265	11.2	299	101
	A11	39.5	14.2	5.0		228	9.1	196	92
	A12	35.5	12.5	4.3		245	7.7	244	104
	Group Average	39.5	13.8	3.4		291	10.4	294	97

Figures 5A, 5B, 5C: Graphs of the pooled hematological data from the two control group animals (A5 and A7). The hematocrit, plasma hemoglobin, platelet count, white blood cell count (WBC), activated clotting time (ACT), and fibrinogen levels are plotted against the autotransfusion cycle number during the experiment. The baseline (pre-procedure parameter values are indicated by "B" and the one day post-procedure parameter values are indicated by "P". All values are plotted as a % of the animal's baseline value (see Table I), except for plasma hemoglobin which is plotted in absolute values. The symbols represent the average value between the experiments and the "error bars" show the range. In each graph, the "circle" connected by lines represent the values measured from samples obtained from the animal. The "squares" represent the values measured from the blood-CPD mixtures collected in the blood bags. The "triangles" represent these same values for the collected blood except that in this case, the data has been corrected for dilution by the added CPD (i.e., these are the values which would have been obtained without dilution by the added CPD).

Control Group

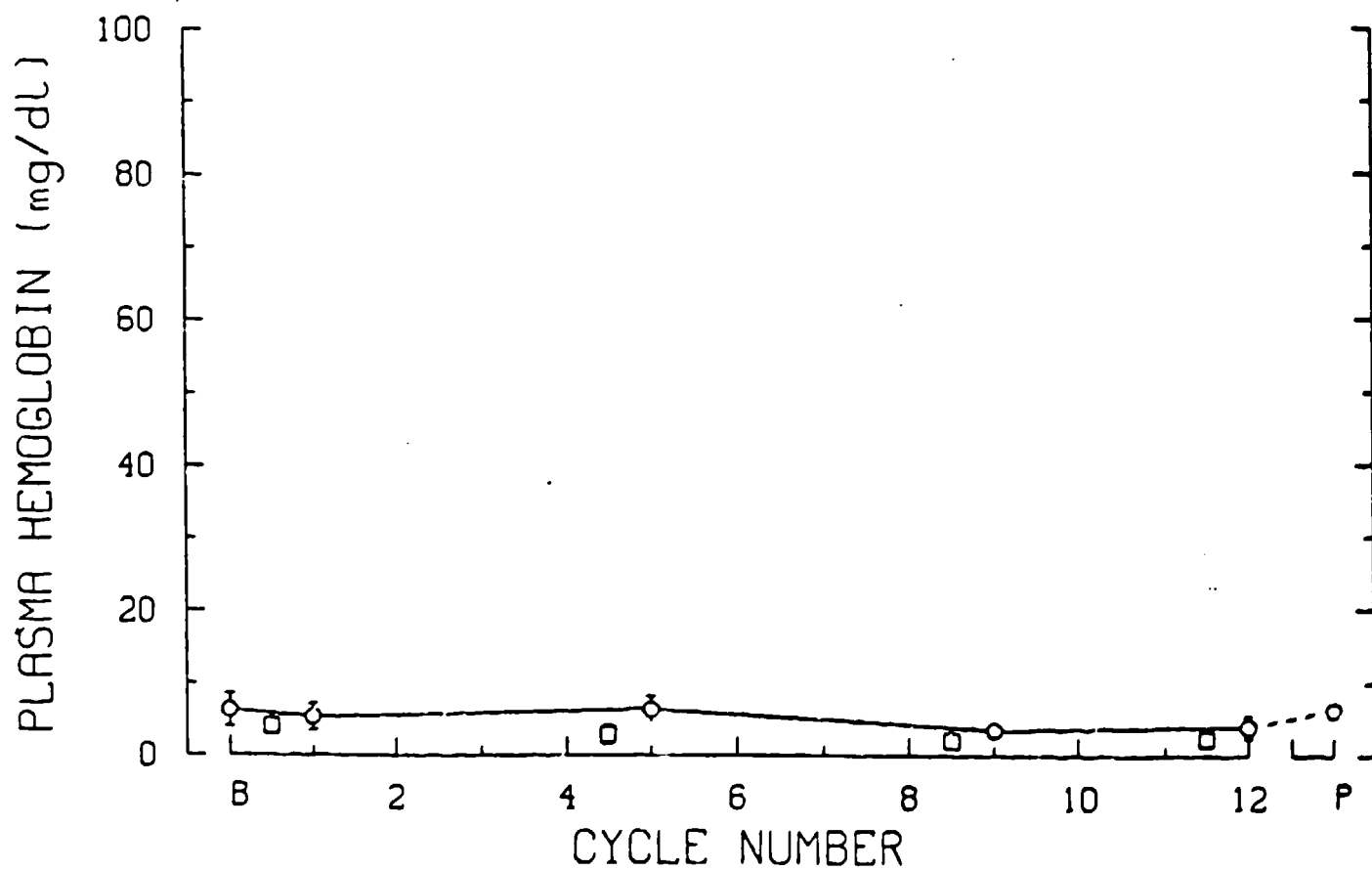
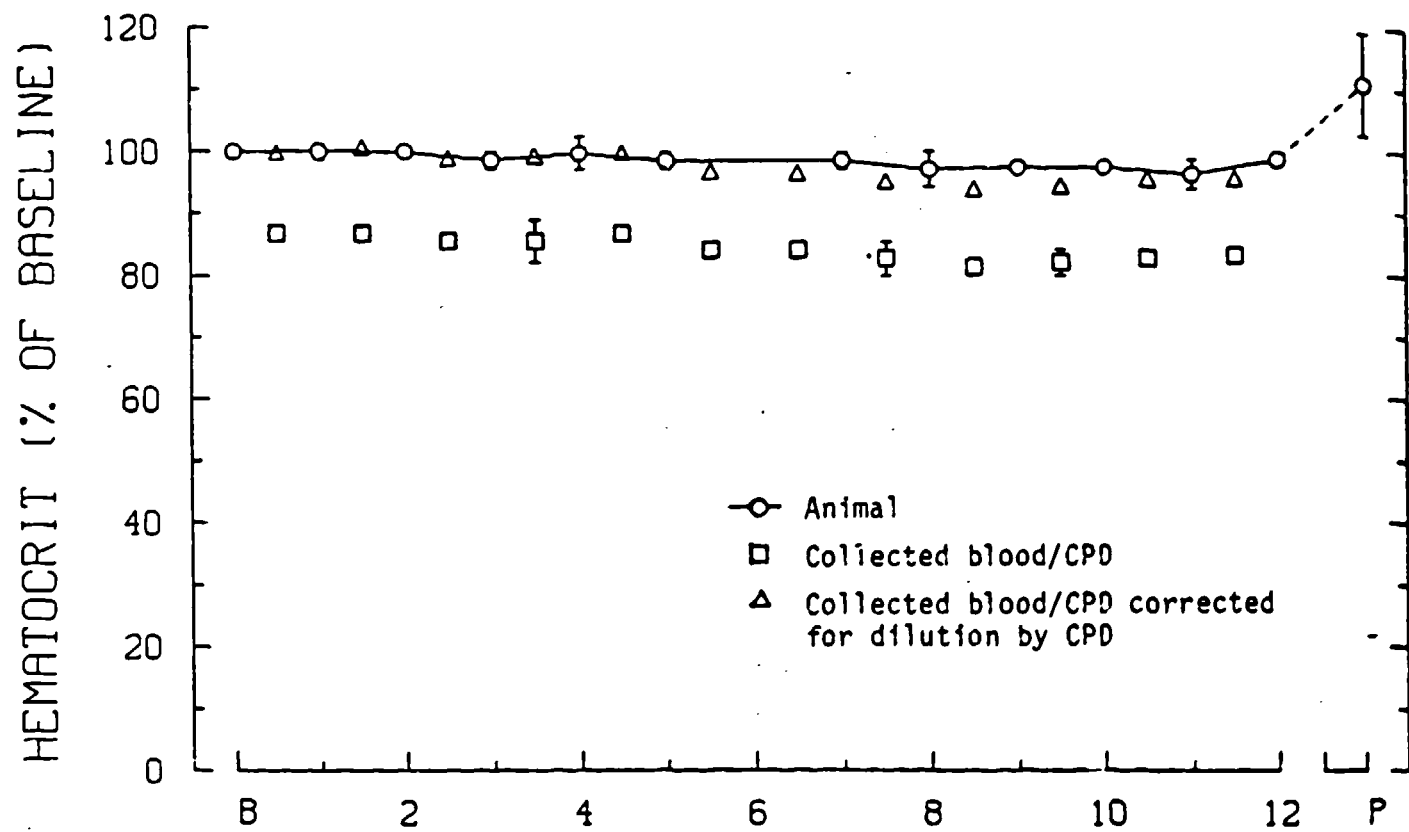


Figure 5A

Control Group

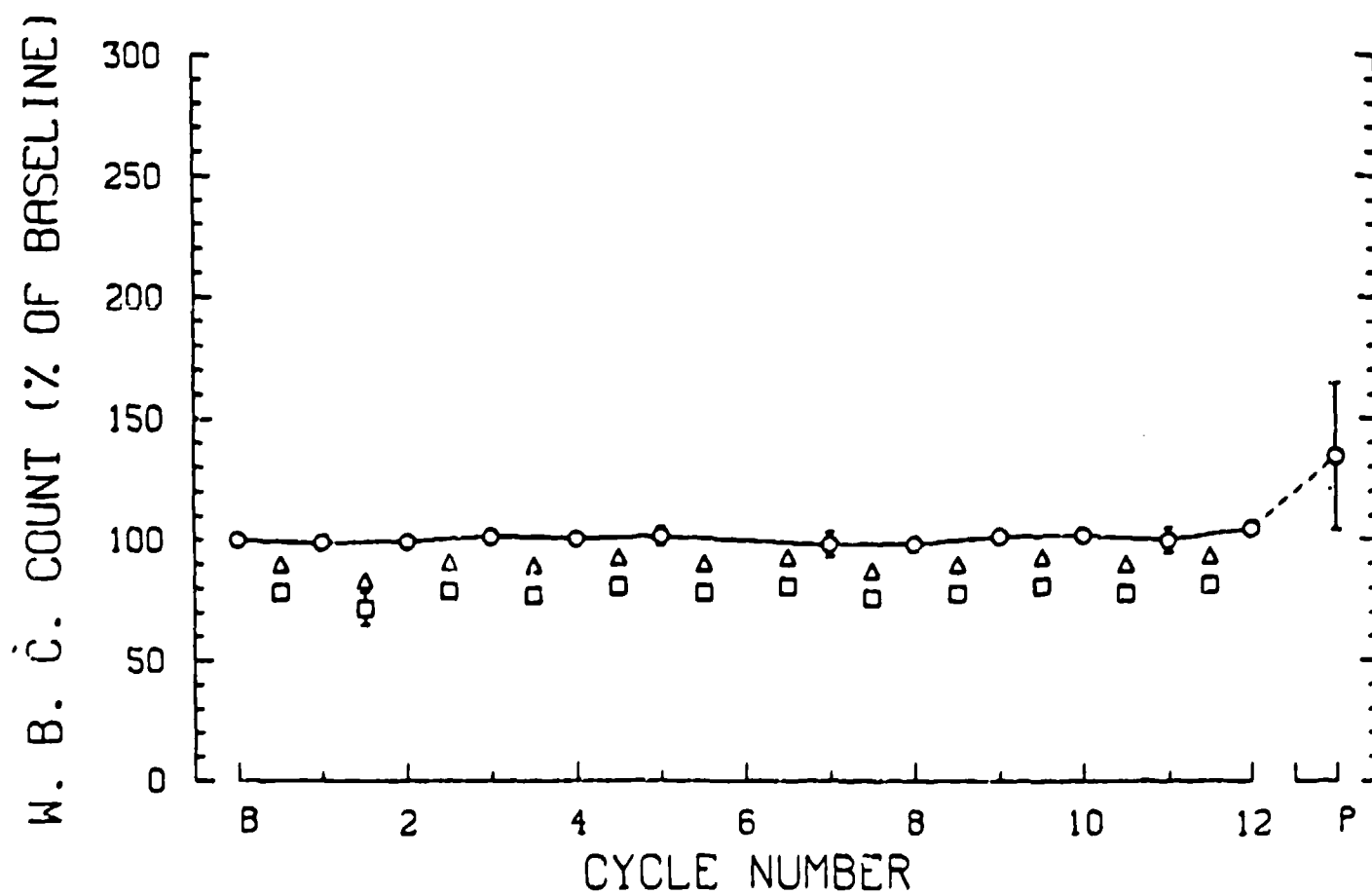
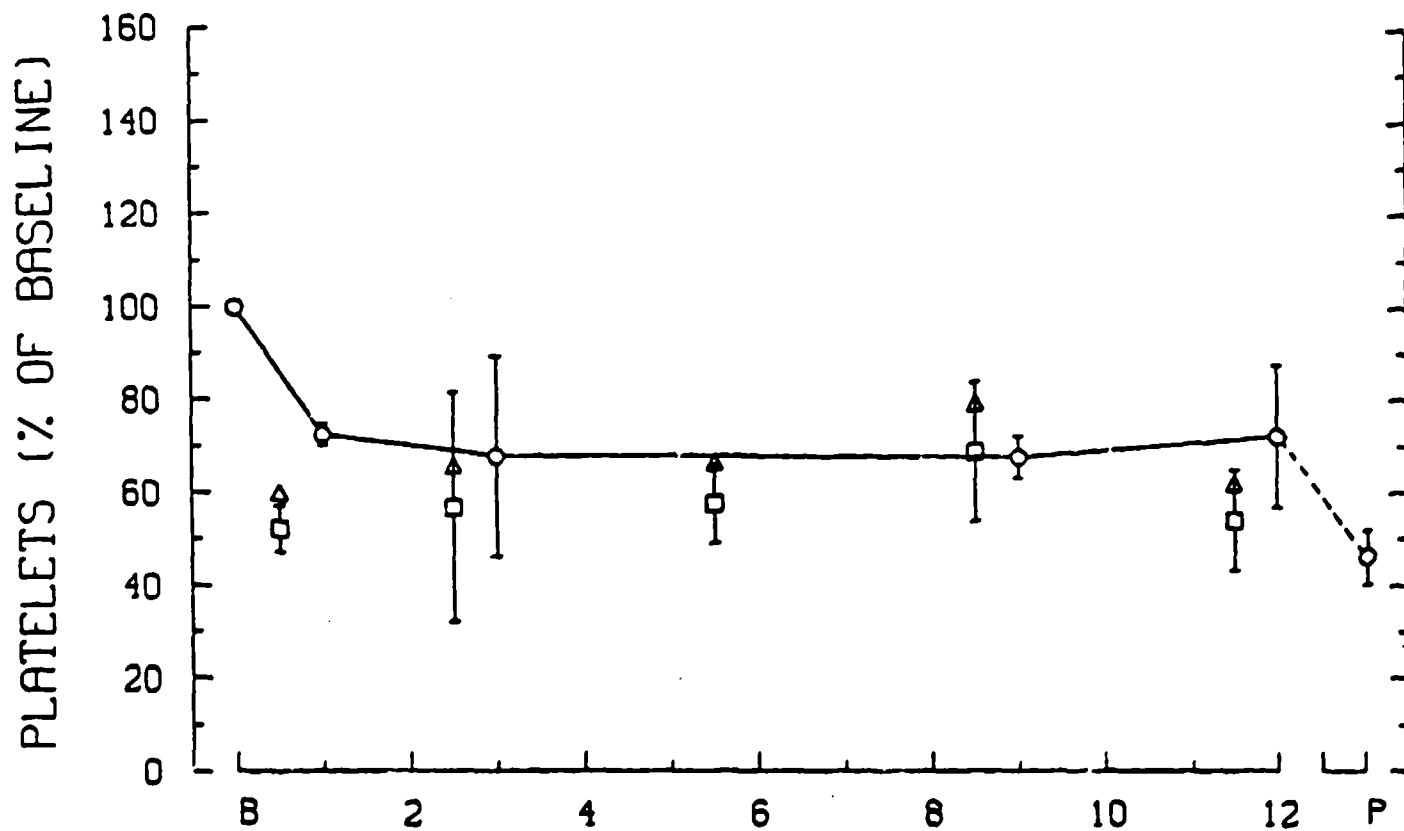


Figure 5B

Control Group

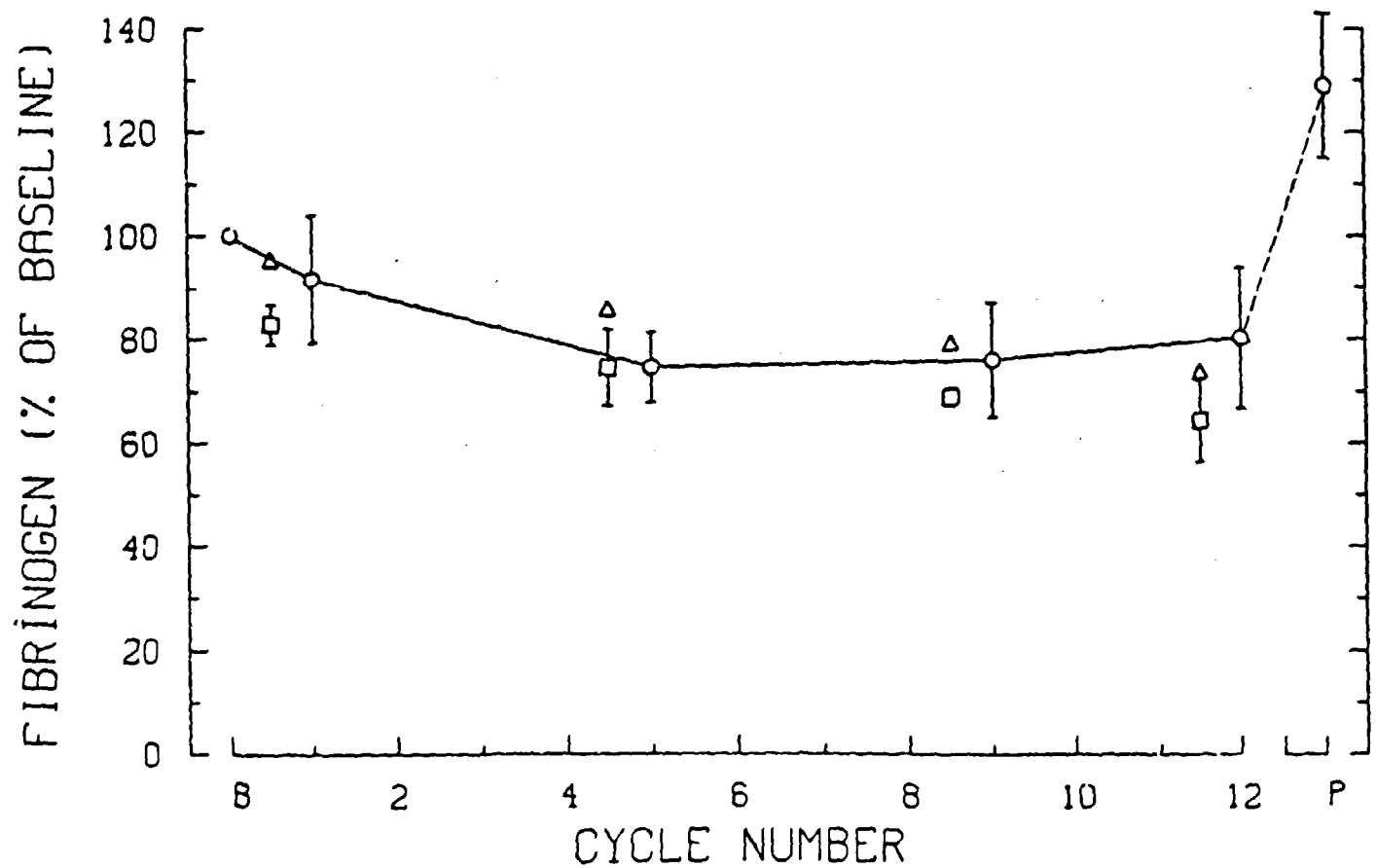
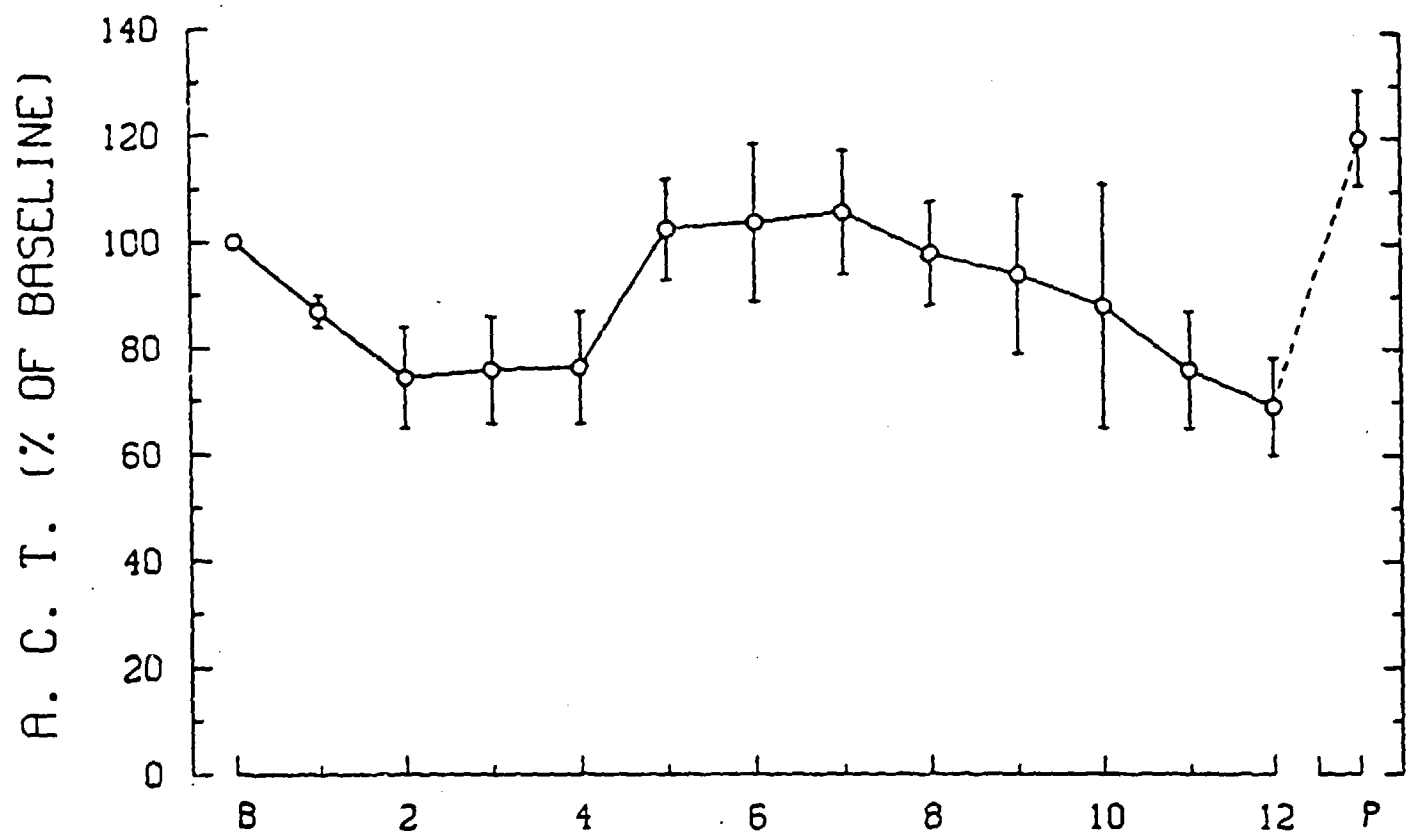


Figure 5C

Figures 6A, 6B, 6C: Graphs of the pooled hematological data from the six ATS group animals (A4, A5, A9, A10, A11, A12). The hematocrit, plasma hemoglobin, platelet count, white blood cell count (WBC), activated clotting time (ACT), and fibrinogen levels are plotted against the autotransfusion cycle number during the experiment. The baseline (pre-ATS) parameter values are indicated by "B" and the one day post-procedure parameter values are indicated by "P". All values are plotted as a % of the animal's baseline value (see Table I), except for plasma hemoglobin which is plotted in absolute values. The symbols represent the mean value from the six experiments and the error bars are the SEM (standard error of the mean). In each graph, the "circles" connected by the lines represent the values measured from the samples obtained from the animal. The "squares" represent the values measured from the blood-CPD mixtures in the salvaged ATS blood. The "triangles" represent these same values for the salvaged ATS blood except that in this case, the data has been corrected for dilution by the added CPD (i.e., these are the values which would have been obtained without dilution by the added CPD).

ATS Group

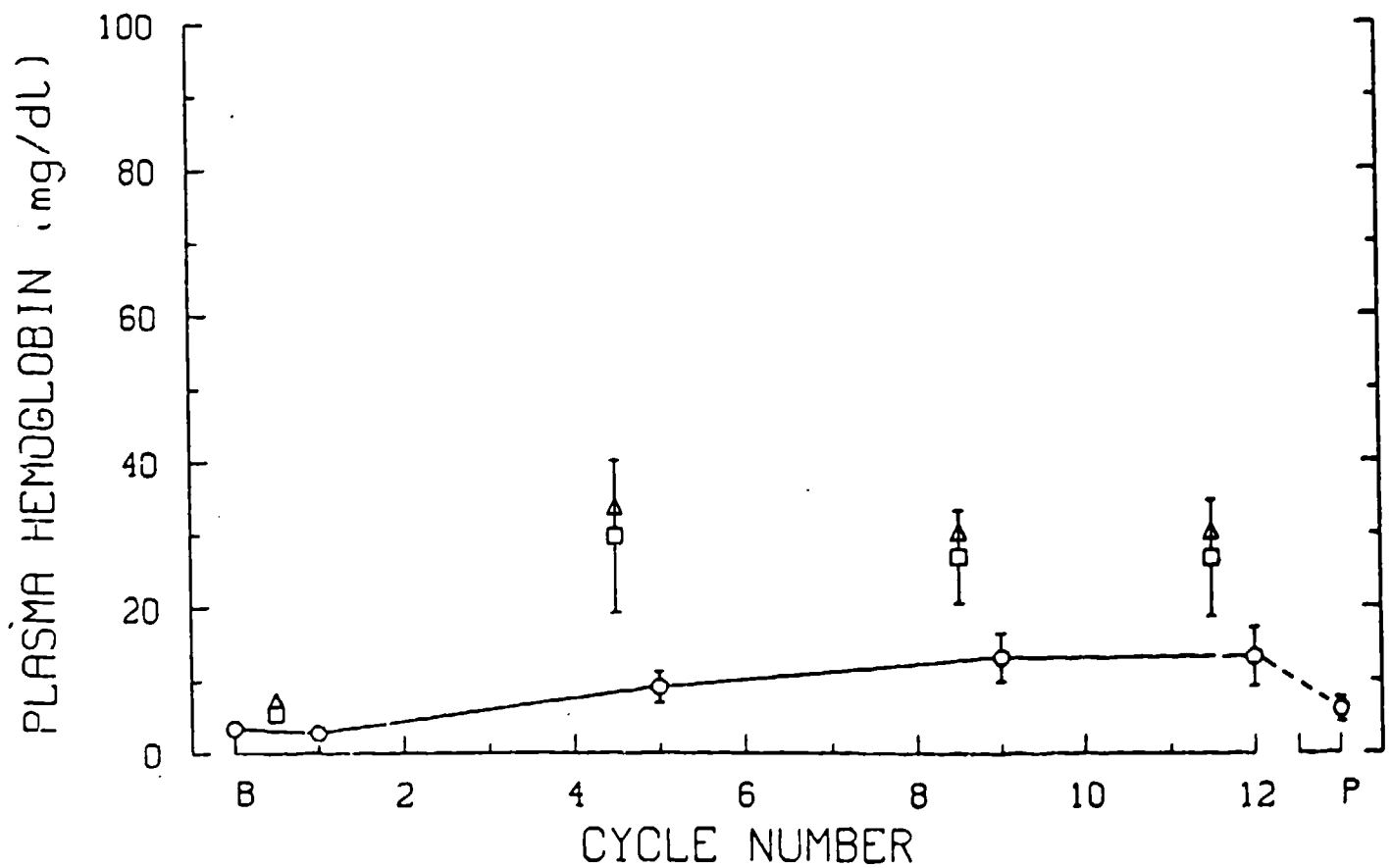
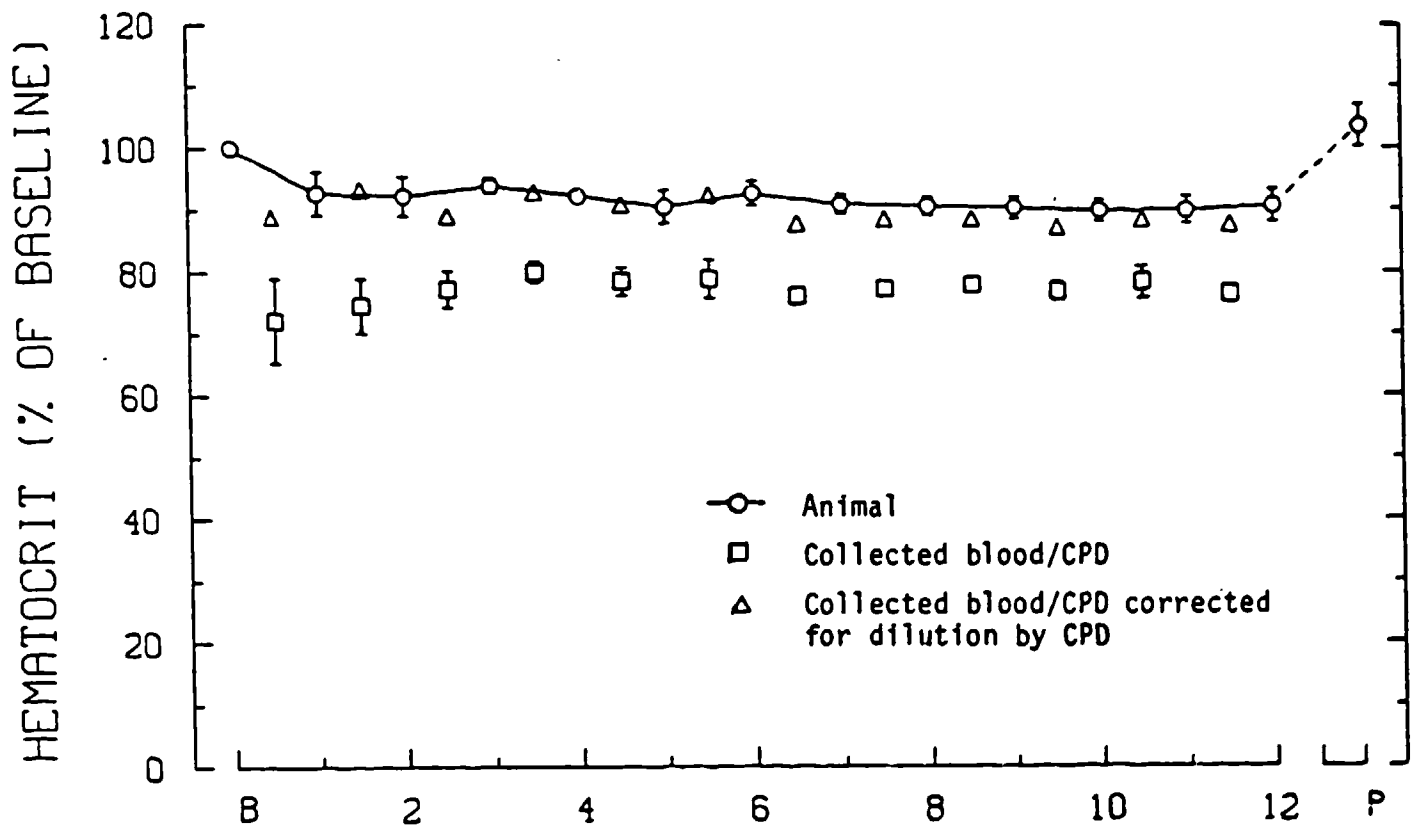


Figure 6A

ATS Group

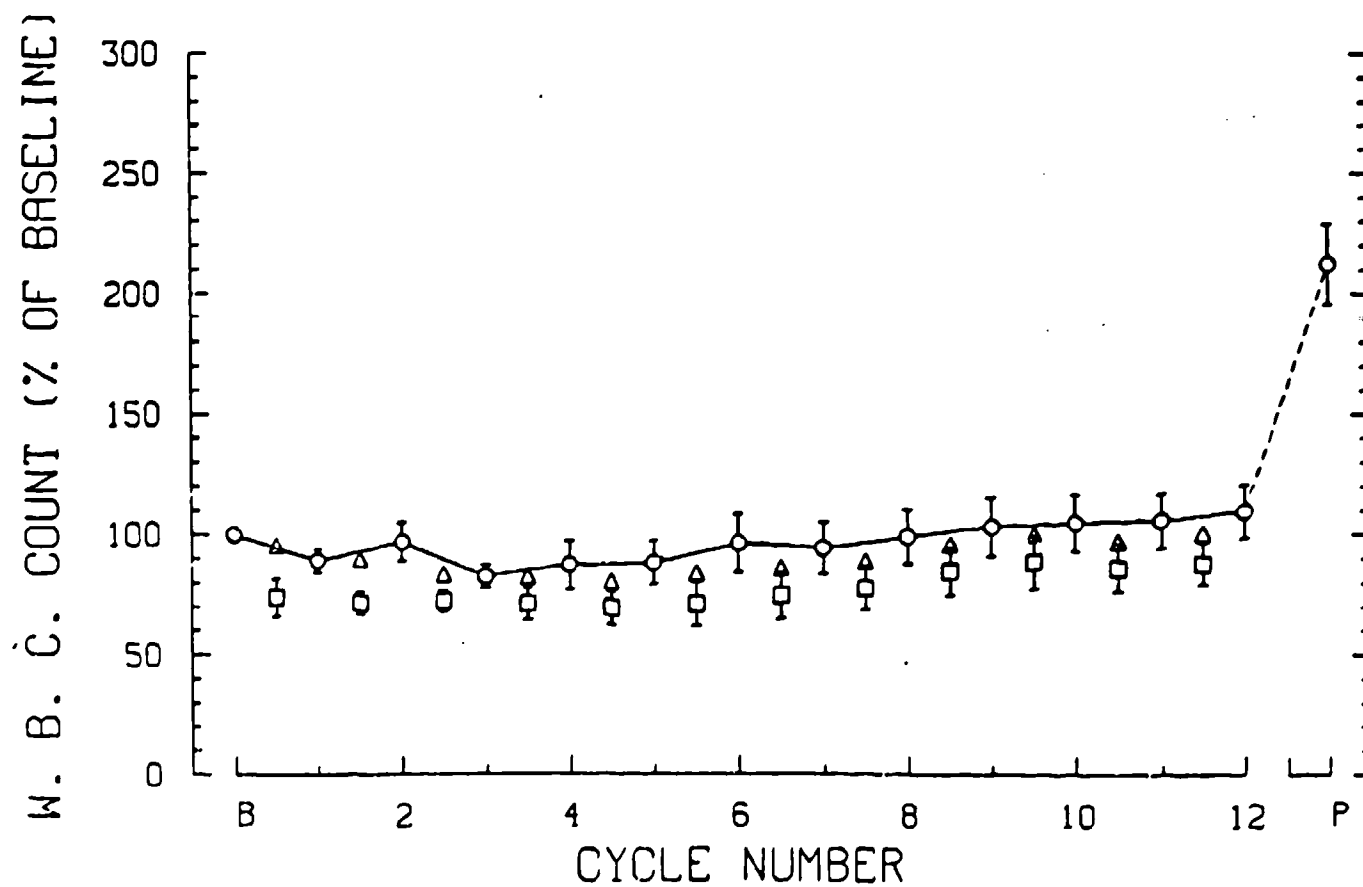
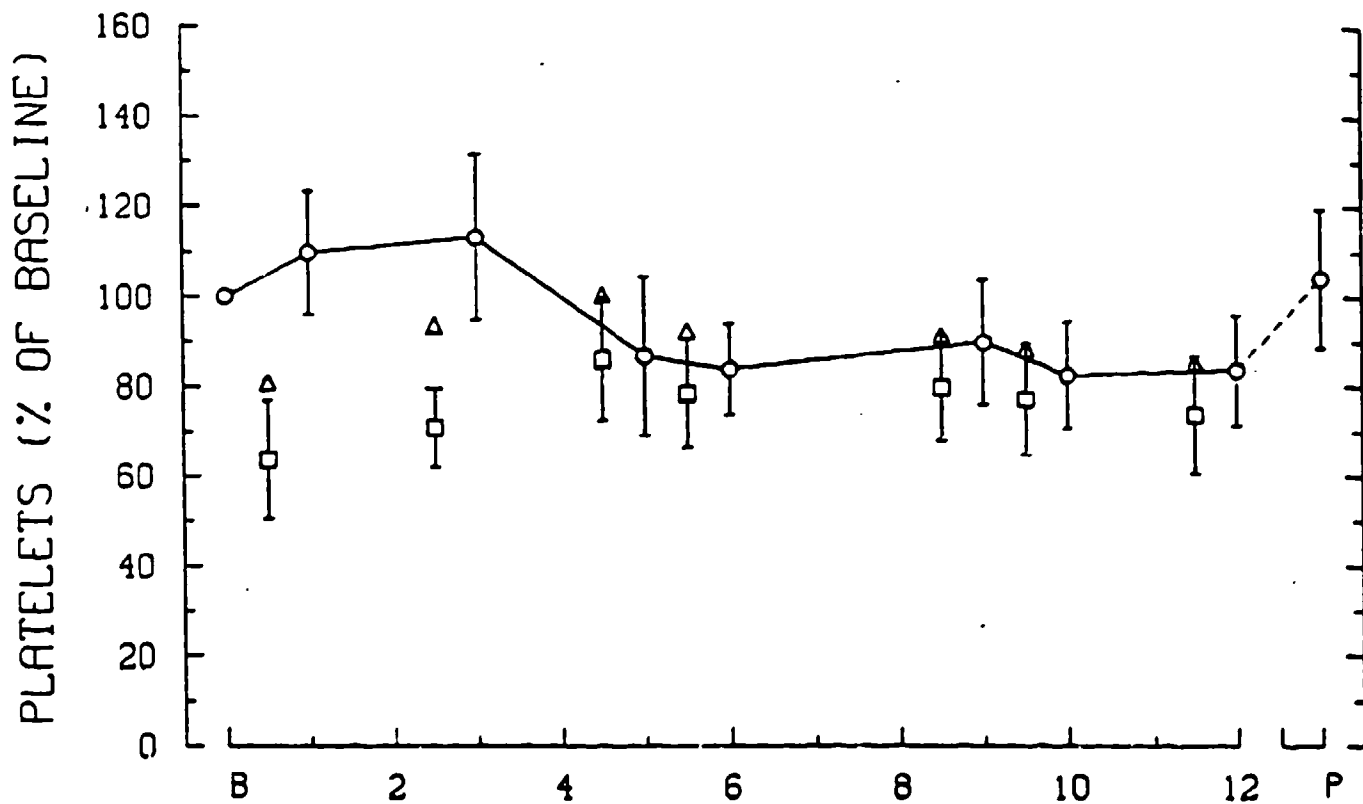


Figure 6B

ATS Group

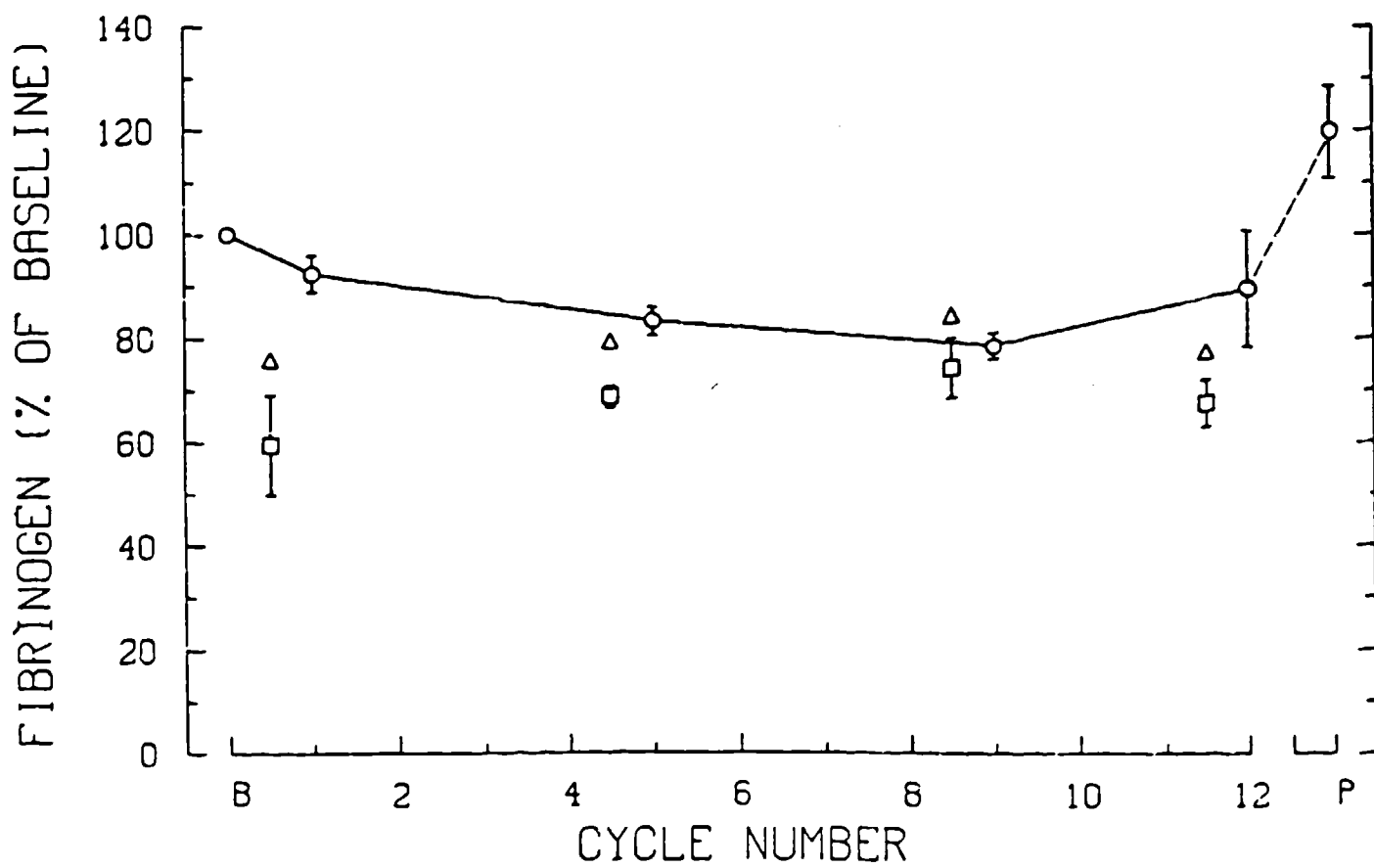
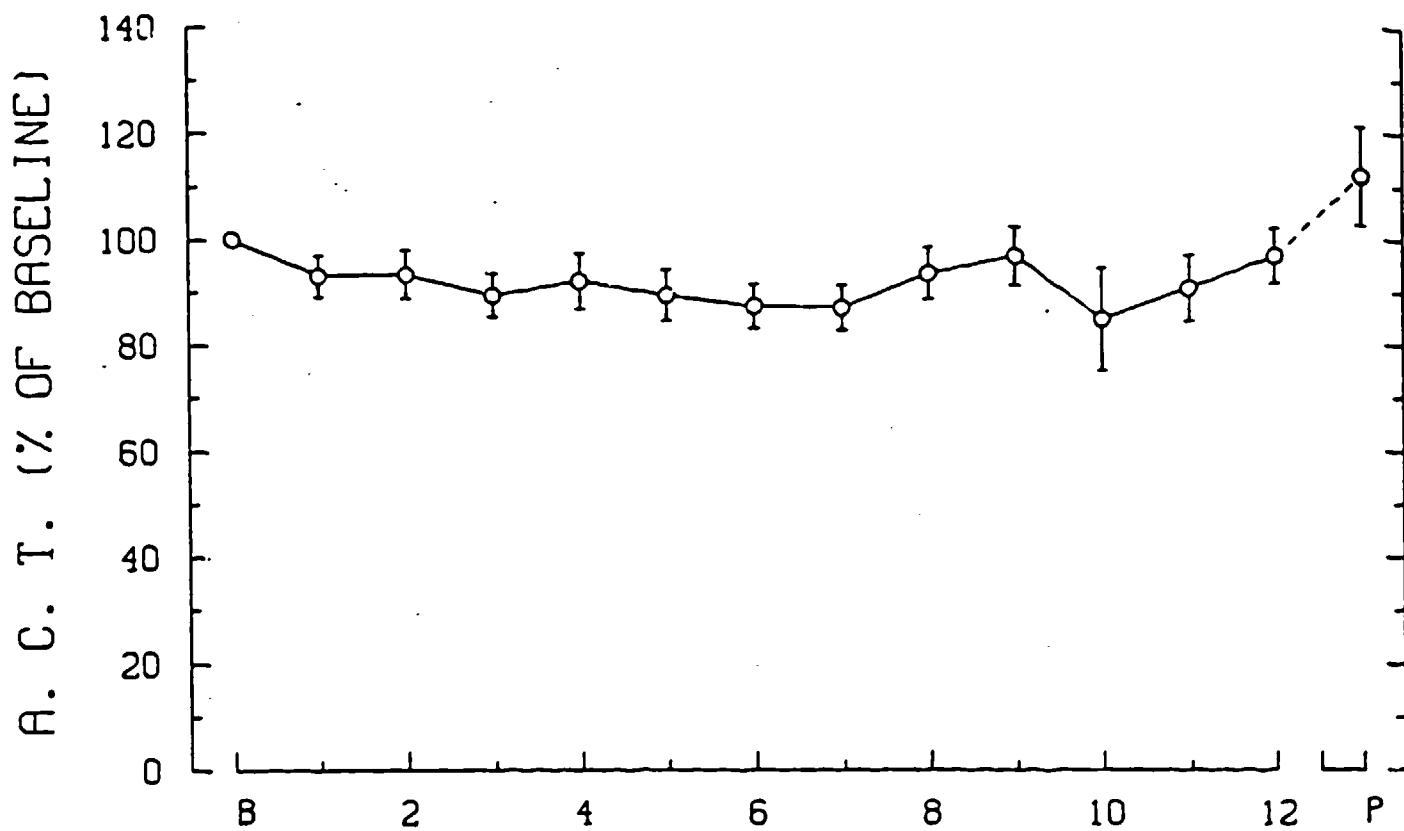


Figure 6C

The more detailed data for all autotransfusion cycles for each of the individual animal experiments are included for reference as Figures A1-A24 in Appendix A. In those graphs, the data are plotted versus time during the experiment (rather than cycle number). Again the "circles" and "squares" represent measurements from blood sampled from the animal and from the collected ATS blood-CPD mixtures, respectively. The "triangles" represent dilution-corrected values for the collected ATS blood-CPD samples.

Blood/Anticoagulant Mixing and Calcium Levels: Anticoagulant was automatically mixed with the blood as it was aspirated. At the conclusion of each ATS (or sham ATS) cycle, the volume ratio (R) of collected blood to added CPD was calculated. These results are given in Figure 7 for the pooled control group and pooled ATS group animals. The ratios for each of 24 control group cycles and 82 ATS group cycles are plotted against cycle number. The desired range for the value of R (5 to 10) is indicated on the graph. In all cases (n=82), the blood/CPD mixing was found to be adequate as measured by the activated clotting time of the salvaged blood which was always found to be greater than 480 seconds, as required by the AAMI/ANSI Standard on Autotransfusion (Hauer and Orr, 1982).

During one of the control experiments (animal A7) calcium gluconate (1 gm) was administered during the second cycle of blood reinfusion despite the maintenance of an acceptable R. During the ATS group experiments, calcium was not required in three of the animals (A10, A11, and A12). In experiment A9, calcium was administered during blood reinfusion for the second and fifth cycles, although R had not gone below a value of 5.8. Similarly in experiment A6, calcium was administered during blood reinfusion for the second, fifth, eighth, and twelfth cycles, although R for this experiment was never below 5.3. In experiment A4, calcium was administered during blood reinfusion for the second cycle which, in this case, had an R of only 1.5 (i.e., too much CPD).

Table II gives the measured total calcium levels for each of the control and ATS group animals. In one control animal (A7) two measurements exceeded the "established reference range" for dogs (8.10-11.30 mg/dl; Vet Path, Teterboro, NJ). In each of three of the ATS group experiments (A4, A6, and A10), one measurement exceeded the reference range by a small amount while in the other three experiments the calcium levels were always within the range. Calcium levels never fell below the range.

Arterial Blood Gases: Arterial blood gases (PO_2 , PCO_2 , and pH) were initially measured for each animal under baseline conditions. Values were also measured from arterial samples obtained from the animal at various times during the experiments. Data obtained from the control group and ATS group animals are given in Tables IIIA and IIIB, respectively.

Device Inspection: At the conclusion of each ATS group experiment, the major ATS device components were cut open and visually inspected. In the six experiments there was only a "very slight" (experiments A6 and A12) or "small amount" (experiments A4, A9, A10 and A11) of small thrombi observed on the inflow surface of the first system filter. The remainder of this system component was always clean. It was not possible to ascertain whether these thrombi formed on the filter or within the blood collection line, or were merely aspirated from the wound. In five of the six experiments (A4, A6, A9, A10 and A12), the interior, tubing, and ports of another portion of the system were all clean. In one experiment (A11) there was a moderate sized non-occlusive thrombus at the origin of the outflow port of this component. In three of the six experiments (A9, A10 and A12), the entire blood micro-filter appeared to be completely clean. In three experiments (A4, A6, and A11), there was only a slight to small amount of clot found at the micro-filter surface just inside the inflow port. The interior of the filter material and the region of the outflow port (patient side) appeared to be clean in all cases.

Figure 7: Blood/CPD volume mixing ratios (R).

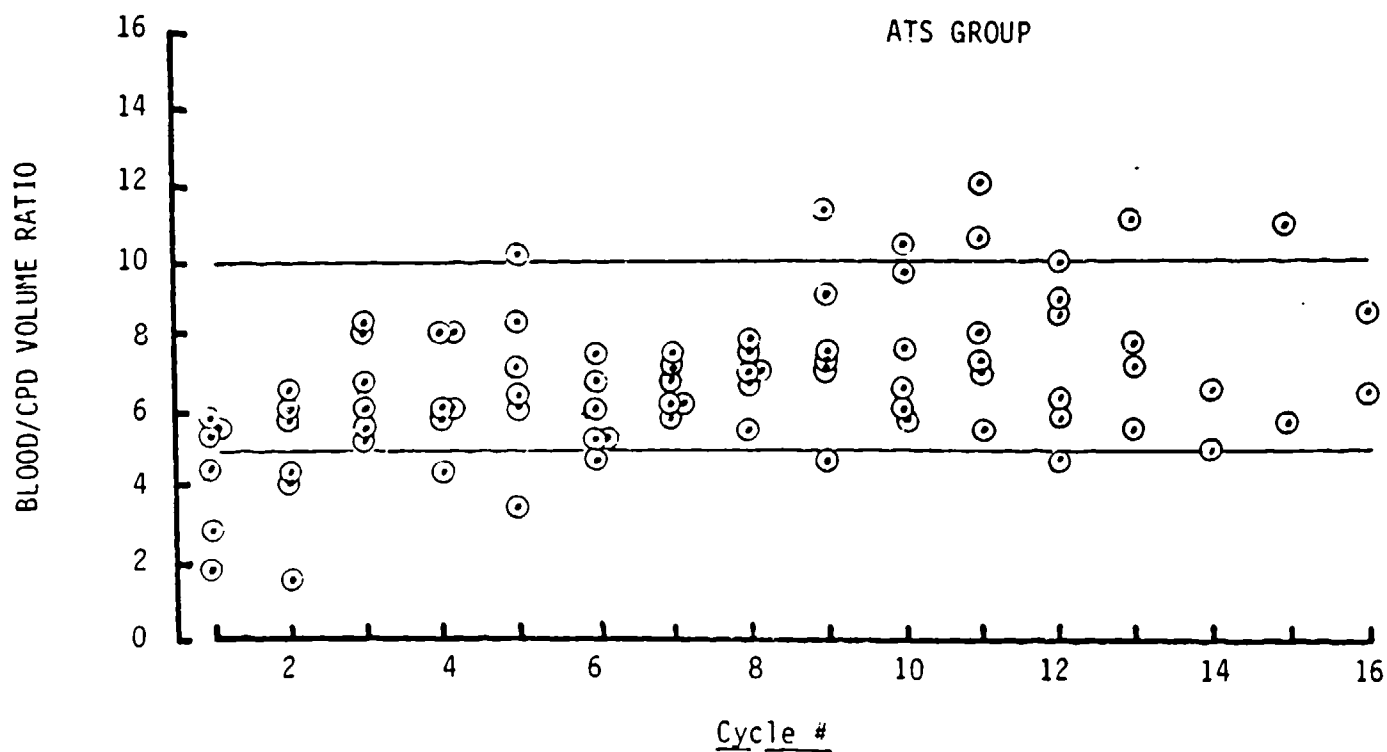
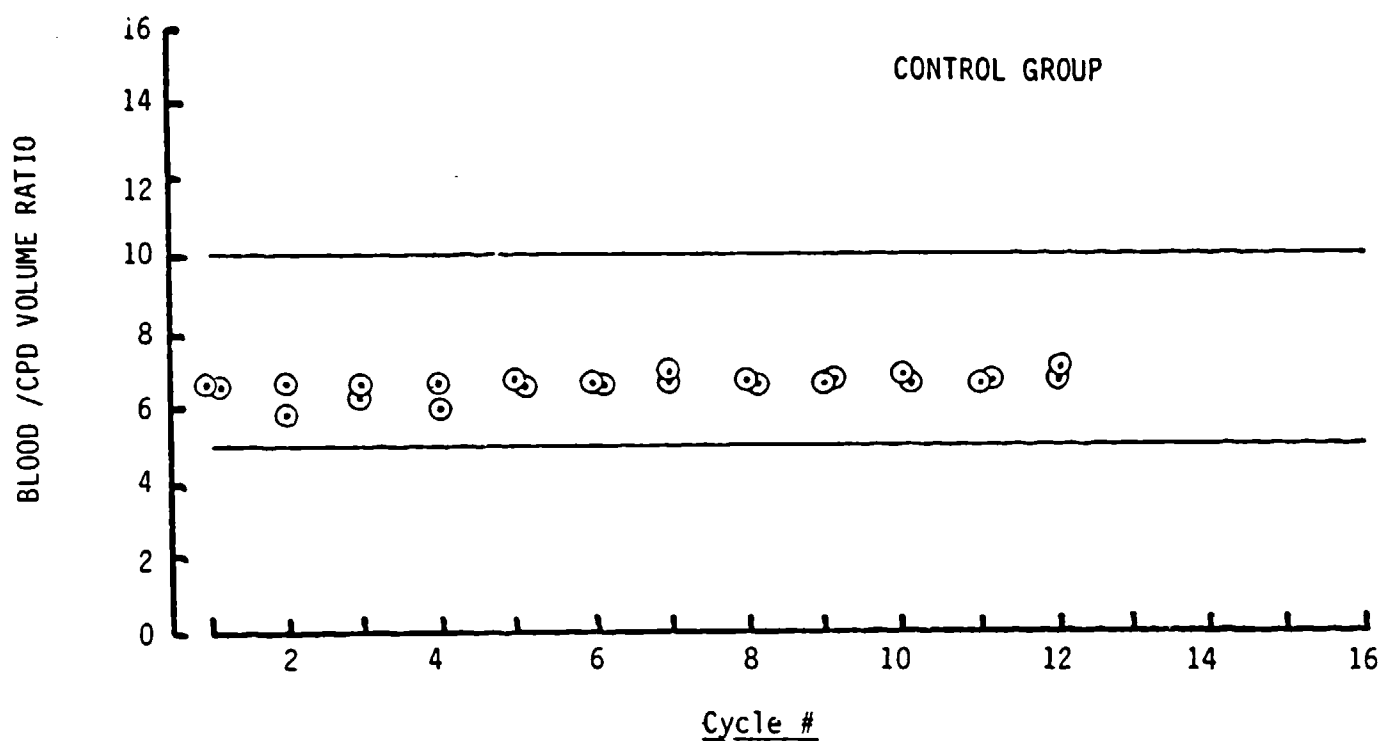


TABLE II: BLOOD CALCIUM LEVELS MEASURED FROM THE ANIMALS

The asterisks indicate excursion beyond
the "reference range" of 8.10-11.30 mg/dl.

CONTROL ANIMALS

<u>Experiment No.</u>	<u>Cycle No.</u>	<u>Calcium mg/dl</u>
A5	B	10.10
	1	10.20
	5	9.70
	9	9.60
	12	9.00
A7	B	9.90
	1	9.90
	5	11.40*
	9	11.90*
	12	11.00
	P	9.20

TABLE II (CONTINUED)**ATS GROUP ANIMALS**

<u>Experiment No.</u>	<u>Cycle No.</u>	<u>Calcium mg/dl</u>
A4	B	10.20
	1	10.80
	5	11.90*
	9	11.20
	12	10.90
	P	9.70
A6	B	10.20
	1	10.30
	5	11.40*
	9	10.40
	12	9.80
	13	11.30
	P	10.30
A9	B	10.30
	B	10.60
	1	9.70
	5	9.60
	9	9.65
	12	8.40
	16	8.70
	P	8.90
A10	B	10.00
	1	11.40*
	5	10.80
	9	8.60
	P	9.10
A11	B	10.20
	1	9.90
	5	9.60
	9	9.20
	12	8.60
	16	8.80
A12	B	9.90
	1	9.70
	5	10.30
	9	10.70
	12	10.40
	13	10.20
	P	9.30

TABLE IIIA

ARTERIAL BLOOD GASES (at 37°C)

CONTROL GROUP ANIMALS

<u>Experiment No.</u>	<u>Time (min)</u>	<u>Cycle No.</u>	<u>PO₂ (torr)</u>	<u>PCO₂ (torr)</u>	<u>pH</u>
5	0	B	140.6	27.4	7.409
	10	B	138.8	25.3	7.398
	182	6	153.6	24.0	7.425
	195	6	152.7	22.7	7.448
	254	9	154.2	23.4	7.446
	312	12	152.7	27.7	7.414
7	2	B	104.3	24.1	7.395
	25	1	109.4	22.6	7.395
	103	5	122.2	21.9	7.284
	254	12	99.0	33.4	7.329

TABLE IIIB

ARTERIAL BLOOD GASES (at 37°C)

ATS GROUP ANIMALS

<u>Experiment No.</u>	<u>Time (min)</u>	<u>Cycle No.</u>	<u>PO₂ (torr)</u>	<u>PCO₂ (torr)</u>	<u>pH</u>
4	45	B	151.4	23.2	7.423
	176	5	155.7	24.5	7.463
	289	9	162.5	24.9	7.481
	360	12	154.8	27.4	7.450
6	3	B	166.9	22.1	7.429
	10	B	166.0	21.0	7.445
	48	1	166.2	24.2	7.456
	142	5	174.9	23.1	7.471
	234	9	172.8	24.4	7.474
	301	12	170.8	25.8	7.480
	324	13	173.9	24.0	7.499
9	0	B	115.8	39.8	7.310
	160	5	118.7	44.8	7.426
	272	9	118.8	41.0	7.341
	342	12	101.1	48.1	7.306
	426	16	113.8	42.1	7.367
10	10	B	138.1	24.7	7.464
	161	5	133.8	45.2	7.406
	284	9	139.2	31.6	7.456
	358	12	145.3	31.4	7.461
11	3	B	162.9	25.8	7.457
	12	B	161.9	24.6	7.467
	151	5	161.1	36.3	7.483
	248	9	154.2	30.5	7.489
	317	12	144.4	35.1	7.446
	372	14	150.7	35.6	7.468
	423	16	110.2	48.9	7.337
12	4	B	182.4	19.9	7.512
	15	B	181.6	19.7	7.506
	25*	B	157.7	24.8	7.441
	104	3	161.2	23.5	7.412
	150	5	160.9	30.4	7.424
	138	5	166.4	27.9	7.442
	251	9	161.8	31.0	7.423
	330	12	161.0	32.3	7.421
	354	13	165.7	33.6	7.405

* Ventilator adjustment.

In one of the control experiments (A5), a small amount of blood clot was found in the blood bag during two cycles. The clot formation was thought to be a result of the relatively slow bleeding rate of this animal. In both control experiments (A5 and A7), there was a small amount of blood clot observed on the filter surface near the inflow port.

Necropsy and Pathology Examinations: The results of the necropsy and pathology examinations are briefly summarized below.

On the day following the procedure, each of the two control group animals was awake, responsive, and drank. The necropsy examinations were generally unremarkable. The pathology reports indicated that all findings were consistent with previously existing chronic conditions, except, perhaps, for splenic changes which were "probably the result of exsanguination and subsequent splenic contraction".

On the day following the ATS group experiments, each of three animals (A4, A6, and A12) was generally alert, responsive and ate and/or drank. A fourth animal (A10) was found to be alert, responded appropriately but slowly, drank normally, but did not stand spontaneously. A fifth animal (A9) was found to be depressed, anorexic, and could not be encouraged to rise. The condition of the sixth animal (A11) is discussed below. As with the control animals, the pathology reports for all of the ATS group animals were generally unremarkable. They indicated that all findings were consistent with previously existing chronic conditions except, as with the controls, for the splenic changes which were probably consistent with the bleeding episodes associated with the experimental protocol.

Operative and post-operative complications occurred in only one ATS case, animal A11. In this case, gross muscle fasciculations were noted towards the end of the operation with a rectal temperature increase from 38.5°C to 38.9°C and an arterial PCO_2 increase intraoperatively. Upon extubation, after 6.7 hours of halothane anesthesia, gross muscle fasciculations continued, a very rapid respiratory rate (120-160/min) was observed, and a rectal temperature of 40.0°C was measured. Within 10 minutes, the rectal temperature increased to 40.6°C . In seven more minutes, the rectal temperature had climbed further to 41.3°C , with a continued rapid respiratory rate, muscle twitching and exhaustion. The animal was electively sacrificed at this time by an overdose of sodium pentobarbital. The results of the necropsy examination were unremarkable. The pathology report indicated that all findings were of "little biological or clinical significance" and appeared to be associated with chronic conditions. It was suggested by the pathologist that certain chronic pulmonary changes and/or the "presence of a foreign body in the lung (a foxtail plant awn found within a bronchial lumen) may explain the post-anesthetic complications that occurred during the recovery phase". The veterinary surgeon attending the case (Dr. Litwak) concluded that the animal's post-operative complications were caused by an episode of malignant hyperthermia.

DISCUSSION

This study represents a preliminary test of an early prototype version of the Thoratec intraoperative ATS. The experiments were conducted under specified surgical conditions with the major objective of obtaining an initial assessment of: the system function under *in vivo* conditions, the effects on the blood of processing and handling by the prototype Thoratec ATS; and the effects of the procedure on animals.

The blood handling function of the device worked quite well. Blood was aspirated at flow rates within the preliminary specification. Upon collection, the blood was readily and quickly deaired in preparation for blood delivery back to the animal.

The hematological effects of the procedure were assessed through sequential measurements of the hematocrit, plasma hemoglobin level, platelet count, white blood cell count, activated clotting time and fibrinogen level. For convenience, this data will be discussed primarily with respect to the overall data as it was pooled from individual experiments.

In the pooled ATS group experiments, the animal's hematocrit decreased during only the first ATS cycle, staying essentially constant at an average of about 90% of the original baseline value over the remaining 11 cycles of the study (Figure 6A). The hematocrit values in the salvaged blood-CPD mixtures were found to be approximately 75 to 80% of the original baseline and roughly 85% of the then current level of the animal's hematocrit. The excellent recovery of red blood cells in the salvaged blood can be seen by correcting for dilution by the added CPD. With this correction, the hematocrit of the salvaged blood was found to be quite close to that of the animal (Figure 6A), except, perhaps for the very first cycle. In fact the difference between the hematocrit levels measured from the animal and the salvaged blood can be accounted for by simple dilution to within an average of 3.5% over the total of 82 autotransfusion cycles in the ATS group experiments (see Figures A7, A10, A13, A16, A19, and A22).

In the control experiments, there was essentially no increase in plasma hemoglobin levels in the animal over the 12 cycles of the experiment (Figure 5A). In contrast there was a progressive increase in plasma hemoglobin levels in the ATS group animals over the 12 autotransfusion cycles (Figure 6A), however, the mean levels in the animal never exceeded 14 mg/dl (range 1.8-31.0 mg/dl; n=28) and returned to baseline levels by the next day. The mean levels in the salvaged blood did not exceed 30 mg/dl, with 80 mg/dl being the highest level found in the entire series. In all cases, these plasma hemoglobin levels were considered to be clinically insignificant (Brizica, 1976). One should be somewhat cautious in comparing these results with other studies because of differences in protocol and species studied. However, it is interesting to note that the plasma hemoglobin levels found in the present study are much lower than those found in the literature particularly with devices utilizing roller pumps; e.g., as high as $1,000 \pm 625$ mg/dl in salvaged blood (Aron et al., 1974) and postoperative elevations of 50 to 600 mg/dl (mean of 175 mg/dl) in 20 patients autotransfused an average of 1.5 liters each (Brenner et al., 1973). Morphologically, the red blood cells in the present study appeared to be normal with only an occasional observation of a crenated cell. Based upon these results, it was concluded that red blood cells have been only minimally affected by the Thoratec ATS process and that the minimal decrease in the red blood cell concentration observed is most likely due to the capture of a certain number of

cells in the filter and on other surfaces of the ATS, and perhaps the destruction of only the most fragile of the circulating red blood cells. A return to greater than baseline hematocrit levels was found by the day following the procedure.

The mean platelet count in the ATS group animals decreased by less than 20% over the course of the experiment and returned to the baseline value by the day following the procedure (Figure 6B). This result, in fact appeared to be better than that seen in the two control experiments (Figure 5B) although, because of the small number of experiments, this comparison must be made with caution. In the ATS group experiments, the recovery of platelets in the salvaged ATS blood was very good, particularly when corrected for dilution by the added CPD. In fact, by the fifth autotransfusion cycle, there appeared to be no further decrease in the average platelet counts below the 80% baseline level.

Over the course of the ATS group experiments, the mean fibrinogen levels in the blood samples taken from the animals did not fall below 78% of the baseline value (Figure 6C). The pattern and magnitude of the change in fibrinogen levels observed in the ATS group (Figure 6C) was very similar to that seen in the control group animals (Figure 5C). There was also very good recovery of fibrinogen in the salvaged ATS blood as indicated in Figure 6C by the levels of the dilution-corrected ATS blood fibrinogen levels.

On the average, the measured activated clotting times of the blood sampled from the animal did not change greatly during the ATS group experiments (Figure 6C). On an individual animal basis, some variation in the ACT was seen during the experiments, but this variation in the ATS group animals (Figure A9, A12, A15, A18, A21 and A24) did not appear to be any greater than that seen in the control group animals (Figures A3 and A6). The measured activated clotting times of blood samples from the total of 82 salvaged ATS blood volumes autotransfused over the course of the six ATS group animal series were always greater than 480 seconds as required by the AAMI/ANSI Standard on Autotransfusion Devices (Hauer and Orr, 1982).

For the pooled ATS group experimental data, the average white blood cell count in blood samples taken from the animals decreased over the course of the first three or four autotransfusion cycles, but did not fall below 80% of the baseline level. From then on, the count increased slowly to approximately 110% of the baseline by the end of the 12th cycle. On the day following the experiment, the average count was up to 212% of the baseline level. This can be contrasted with the control group experiments (Figure 5C) in which the white blood cell counts from the animal remained essentially constant throughout the experiment with an increase to approximately 134% of the baseline level by the day following the procedure. In this respect, it is important to note that the prototype ATS devices used in the ATS group experiments were not sterilized because of practical limitations associated with the early prototype nature of the devices (such limitations will be corrected for subsequent experiments). In the control experiments, the blood bags, blood filter, and blood reinfusion line were sterile commercial devices. With the use of non-sterile ATS devices, it was decided that, for convenience, neither the ATS group or control group experiments would be conducted under sterile surgical conditions (although sterile procedures can be routinely carried out at Thoratec's Surgical Laboratory). With this explanation, the increased WBC count during and after the ATS group experiments is not surprising. With respect to the post operative complications encountered with animal A11 (see Results section above), it must be considered that a pyrogenic reaction associated with the non-sterile device and procedure may have been the cause. However, the attending veterinary surgeon (Dr. Litwak) concluded that an episode of malignant hyperthermia was the most likely

explanation for the complication, and that the Thoratec ATS procedure per se was not a factor.

Probably more significant than the actual WBC count levels is the fact that there appears to have been very good recovery of WBC's in the salvaged ATS blood (Figure 6B). This was evident from the fact that the WBC levels in the salvaged blood, after correction for dilution by the added CPD, were generally quite close to the WBC levels measured from blood samples drawn from the animal. The recovery of WBC's in the ATS group experiments was similar to that seen in the control group experiments (Figure 5B).

As discussed above, these in vivo experiments included serial measurements of the number of platelets, concentration of fibrinogen and the screening test of measuring the activated clotting time. Inspection of this data from individual experiments (see Appendix A) shows that there was some degree of variation from one animal to another in the direction and degree of change in these parameters. This variation was seen in the control group as well as in the ATS group experiments and are to be expected. Anesthesia, the stress associated with a surgical procedure, hemorrhage, and contraction of the spleen are all known to cause wide variations in response from one animal to another (Rutherford et al., 1966; Ljungquist, 1970).

Over the full 12 cycles of both the ATS group and control group experiments, an overall decrease in platelet number, activated clotting time and fibrinogen concentration all indicated some activation of the coagulation system. On stained blood smears, aggregates of platelets were observed in both groups. A screening test for soluble fibrin monomer and/or fibrin split products using 1% protamine sulfate also indicated the probability of some generation of thrombin. Such results were to be expected. The technique of autotransfusion has associated with it some activation of the coagulation system by blood contact with extravascular tissue and foreign surfaces. In our studies, the salvaged blood was obtained from a pocket that allowed exposure to extravascular tissue, and undoubtedly tissue thromboplastin, as well as to the various foreign surfaces of the transfusion systems. However, it is important to note that the control animals showed comparable changes in the coagulation parameters measured, indicating that blood salvage using the Thoratec ATS does not appear to have increased the level of the limited changes over that seen in the control group. At no time did the platelets or fibrinogen approach levels that would compromise the hemostatic mechanism in the animal. We did not measure platelet function but no excess of bleeding or oozing at the surgical sites was observed. By the day following the procedure, the ACT, platelet counts, fibrinogen levels (as well as hematocrit and plasma hemoglobin) all returned to near baseline values. Using a Sorenson Autotransfusion System in studies with dogs, Moore et al. (1980) also observed a return of clotting times and fibrinogen levels 24 hours following autotransfusion, however, platelet levels in their study did not recover, continuing to fall during their post autotransfusion period.

In the 82 ATS cycles conducted, the measured values of R (the volume ratio of blood aspirated to CPD added by the ATS) were found to lie predominantly within the desired range of 5 to 10. However, there were occurrences in which R was found to be outside the range, either above (n=7) or below (n=11). This variation in R was attributed to three factors: a durability problem of one component of the special CPD delivery system of the then current prototype Thoratec ATS; some remaining restrictions in the type of aspiration technique that could be properly accommodated by the system; and the requirement of some initial adjustment of the CPD flow resistance particularly during the beginning of the first experiment (A4). Even with these variations, the salvaged ATS blood/CPD mixtures all (n=82) had activated clotting times greater than

480 seconds, as desired. Since these experiments, there has been continued improvement in the function of the CPD delivery system being developed as part of Thoratec's program for a commercial version of its ATS. Thus, with these advances: the previously deficient component has now been replaced with a vastly superior part that has not shown any problem with durability; the remaining restrictions in the type of aspiration technique have been substantially reduced (if not effectively eliminated); and the adjustments to the CPD flow resistance no longer appear to be necessary. Continued evaluation of these significant improvements is in progress.

In all control and ATS group experiments, the mean arterial blood pressure remained generally constant. This contrasts with results obtained by Rakower, et al., (1974) in which the mean arterial blood pressure in autotransfused dogs tended to fall despite massive infusions of crystalloid. In the present experiments, there was typically a 10-20 mm Hg transient decrease in the mean arterial blood pressure during the bleeding episode. Upon blood reinfusion, three types of blood pressure response were typically observed. In some cases, the delivered blood volume resulted in an increase in blood pressure, with no decrease observed. In other cases, the blood pressure decreased transiently during blood reinfusion, but then recovered spontaneously within minutes. In a few cases (once in the 24 control cycles and 6 times in the 82 ATS cycles) the blood pressure decreased somewhat more than usual during blood reinfusion. This was considered to be an indication of hypocalcemia and 1.0 gram of calcium gluconate was administered. In these cases, the blood pressure always responded quickly, substantially recovering within one to two minutes. The observed responses to reinfusion of the citrated blood is not specific to the autotransfusion procedure as similar responses were seen in the control group animals. Furthermore, the present finding of a transient hypotension that could be rapidly reversed by calcium administration is consistent with studies in man in which it was found that a significant but transient hypocalcemia can accompany the transfusion of normally citrated banked blood (Denlinger et al., 1976). Others (Olinger et al., 1976) demonstrated effects of hypocalcemia and an associated acute myocardial depression with the rapid transfusion of as little as one unit of normally citrated blood. The effects depend upon the quantity of citrated blood infused, the speed of infusion, and the condition of the recipient. Olinger et al. (1976) recommend administration of calcium during massive and/or rapid homologous transfusions. A similar practice could readily be implemented in the case of autotransfusion procedures. In our experiments, we had little difficulty in avoiding problems with hypocalcemia during the 24 control group and 82 ATS group transfusions.

Finally, the reports of the comprehensive necropsy and pathology examinations indicated that all findings were associated with chronic conditions considered to be unrelated to the experimental procedure, with the exception of evidence of splenic contraction which was seen in both control and ATS animals, presumably due to the bleeding episodes inherent in the protocol. We concluded that the animals tolerated the autotransfusion procedure quite well.

SUMMARY: The results of our initial in vivo tests of the Thoratec prototype ATS are considered to be very positive. The overall blood handling function of the system was found to be convenient and efficient. The measured values of hematocrit and plasma hemoglobin indicated only a minimal effect of the ATS procedure on the red blood cells. Additionally, there appeared to be very good recovery of platelets, white blood cells, and fibrinogen in the salvaged blood, with relatively small changes in these measured hemostatic parameters which were not very different from the changes observed with the control group animals. By the day following the experiment, all measured parameters returned to near baseline levels, except for the white blood cell counts which were elevated as expected. The blood/CPD mixing function of the prototype

Thoratec ATS provided the desired levels of activated clotting time and mixing ratios which were predominantly within the desired range despite some variation. Subsequent system improvements appear to be improving this system function substantially. The requirements for calcium administration during an autotransfusion procedure are likely to be essentially the same as for bank blood transfusion; i.e., with rapid and massive transfusions, calcium administration may be indicated.

VI. PHASE I SUMMARY AND CONCLUSIONS

PHASE I PROGRAM SUMMARY

During the six-month Phase I feasibility research and development program, the following tasks were accomplished:

- (1) The specific requirements of the DoA for autotransfusion were preliminarily identified through early discussions with DoA medical and bioengineering personnel. The key issue of the "logistics of autotransfusion" was identified and investigated. These discussions also included bench demonstrations and preliminary evaluation of the function of the basic prototype Thoratec ATS.
- (2) A preliminary set of product specifications and an overall system design was generated so as to meet the requirements of the DoA, with particular attention given to the logistics issues.
- (3) A "working" prototype model of a proposed DoA version of the basic Thoratec ATS (the DoA-ATS) was designed and fabricated based upon tasks 1 and 2, above. This prototype embodied the key design features of being completely disposable and self-contained, and having system collapsibility (including a collapsible blood reservoir and IV-type pole support) for packaging. This prototype was demonstrated to DoA personnel in two Thoratec presentations.
- (4) A preliminary series of in vivo tests in animals was conducted with the then current basic Thoratec ATS. The objectives were to provide an early assessment of the prototype Thoratec device, with particular attention given to evaluating: functionality under surgical conditions; and the effects of processing blood through the prototype ATS on the animal and his blood.

PHASE I PROGRAM CONCLUSIONS

From the results generated from the accomplishment of the above tasks, we have concluded overall that the basic prototype Thoratec ATS has design and performance characteristics which are extremely favorable to the military application, and that the Thoratec ATS is well suited for adaptation, through appropriate system design modifications, to meet the specific needs of the military use and combat environment. More specifically we have concluded that:

- (1) The enormous and uneven demands for blood during combat, the significant logistics problems of transporting and storing homologous blood, the serious potential for blood shortages for treating combat casualties, the complications of bank blood transfusions, and the significant advantages of fresh autologous blood, all suggest a potentially vital role in the military for intraoperative autotransfusion if a system can be developed to meet the specific needs of the military and combat environment.

- (2) The basic Thoratec ATS provides a sound basis from which to derive a practical system for military use. The Thoratec design already provides a combination of features and functionality which should be very valuable to the military application, and which has not been previously available with other devices.
- (3) The preliminary collapsible Thoratec DoA-ATS design generated during Phase I appears to be properly addressing the specific needs of the military application, particularly the key issue of logistics.
- (4) The basic Thoratec ATS is well suited for adaptation according to the preliminary product specifications and collapsible system design.
- (5) Based upon our preliminary in vivo animal tests of the current version of the Thoratec prototype ATS, we found that:
 - The overall blood handling function of the device is convenient and efficient.
 - With the test protocol used, the damage to the red blood cells by the operation of the ATS was minimal, the recovery of blood components in the salvaged blood was very good, and the relatively small changes in measured hemostatic parameters were not very different from those observed with the control group of animals.
 - The automatic blood/CPD mixing function of the prototype Thoratec ATS was good, providing the desired levels of activated clotting times. Subsequent improvements in this unique proprietary system appear to provide additional improvements in this function.
 - The animals tolerated the Thoratec ATS procedure , with a recovery to, or near, baseline blood parameter values by the day following the procedure.
 - The requirements for calcium administration during the Thoratec ATS procedure appear to be similar to that for bank blood transfusion.
- (6) The collapsible IV pole already developed in prototype form during Phase I (see Section IV) may have substantial value to the Army as a product in its own right.

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APPENDIX A

GRAPHS OF HEMATOLOGICAL DATA FOR EACH INDIVIDUAL ANIMAL

For each of the control and ATS group animals, the hematocrits, plasma hemoglobin levels, platelet counts, white blood cell counts (WBC), activated clotting times (ACT), and fibrinogen levels are plotted against time (min) during the experiment. The baseline (pre-ATS) parameter values are indicated by "B" and the one day post-procedure parameter values are indicated by "P". All values are plotted as a % of the animal's baseline value (see Table A1), except for plasma hemoglobin which is plotted in absolute values. In each graph, the "circles" connected by lines represent the values measured from samples obtained from the animal. The "squares" represent the values measured from the blood-CPD mixtures salvaged by the ATS (or sham ATS procedure). The "triangles" represent these same values for the salvaged blood except that in this case, the data has been corrected for dilution by the added CPD (i.e., these are the values which would have been obtained without dilution by the CPD). The control group includes animals A5 and A7, while the ATS group includes animals A4, A6, A9, A10, A11, and A12.

TABLE AI

BASELINE BLOOD PARAMETER VALUES

	Animal No.	Hematocrit	Hemoglobin (g%)	Plasma Hemoglobin (mg/dl)	Platelets (X10+5)	WBC (X10+3)	Fibrinogen (mg/dl)	ACT (sec)
C O N T R O L	A5	41.0	14.4	8.5	280	16.8	403	99
	A7	35.0	12.0	4.0	325	14.9	362	92
	Group Average	38.0	13.2	6.3	303	15.9	383	96
A T T E N T I O N G R O U P	A4	37.0	13.4	2.0	393	11.6	228	76
	A6	33.5	12.0	2.0	343	11.0	308	94
	A9	44.0	15.6	3.0	273	11.7	388	117
	A10	41.5	14.9	4.3	265	11.2	299	101
	A11	35.5	14.2	5.0	228	9.1	196	92
	A12	35.5	12.5	4.3	245	7.7	344	104
	Group Average	38.5	13.8	3.4	291	10.4	294	97

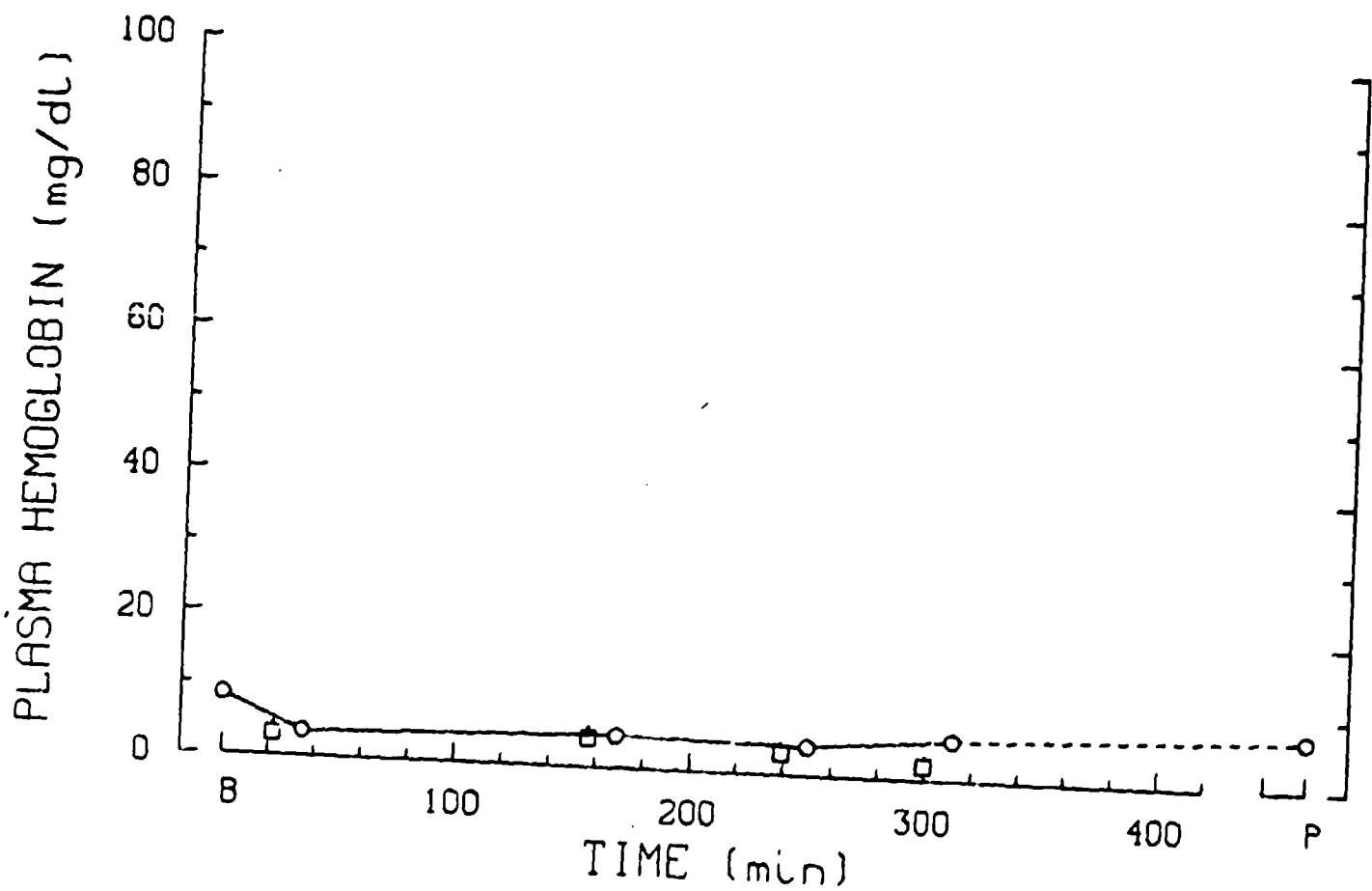
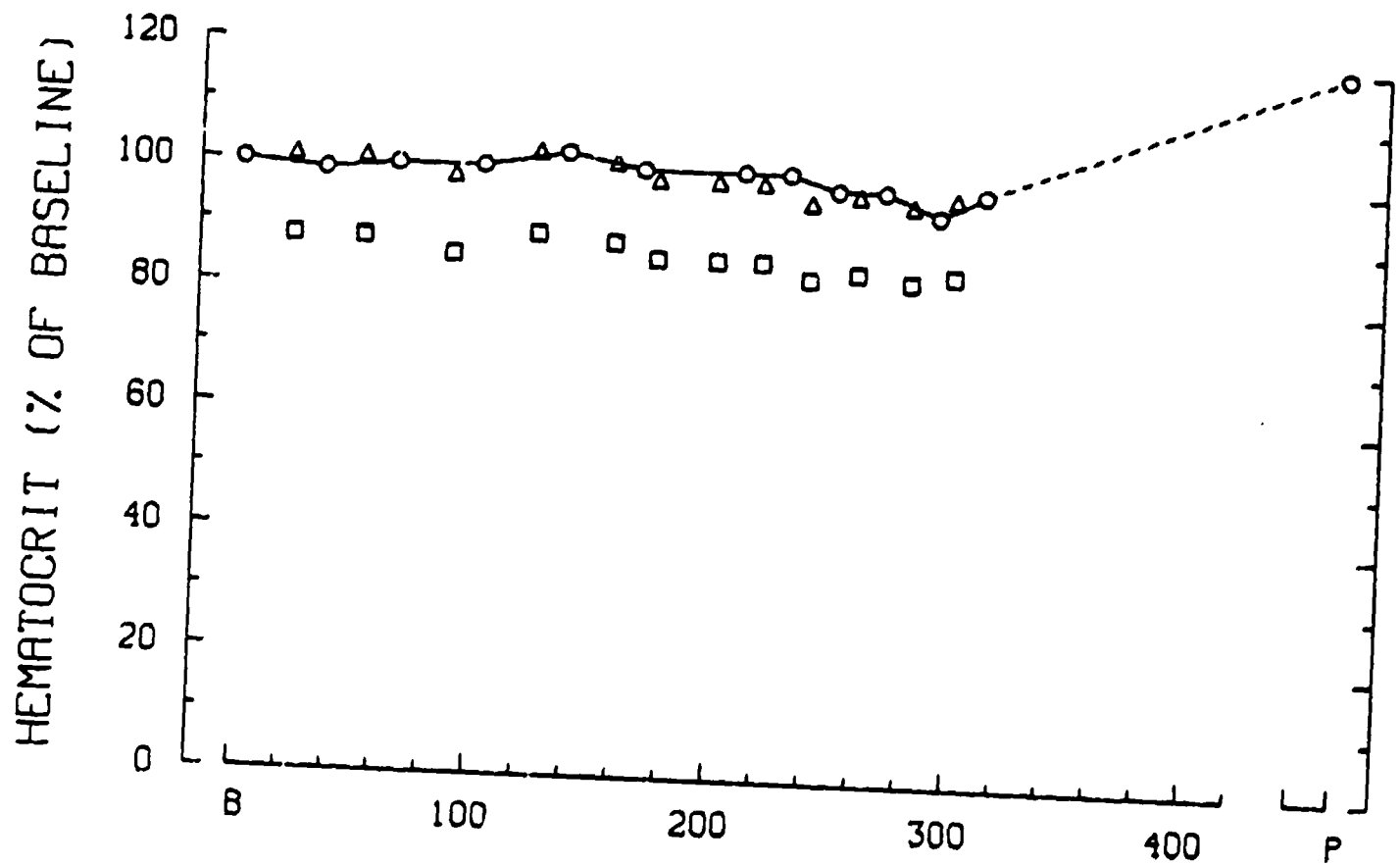


Figure A1: Control Animal A5

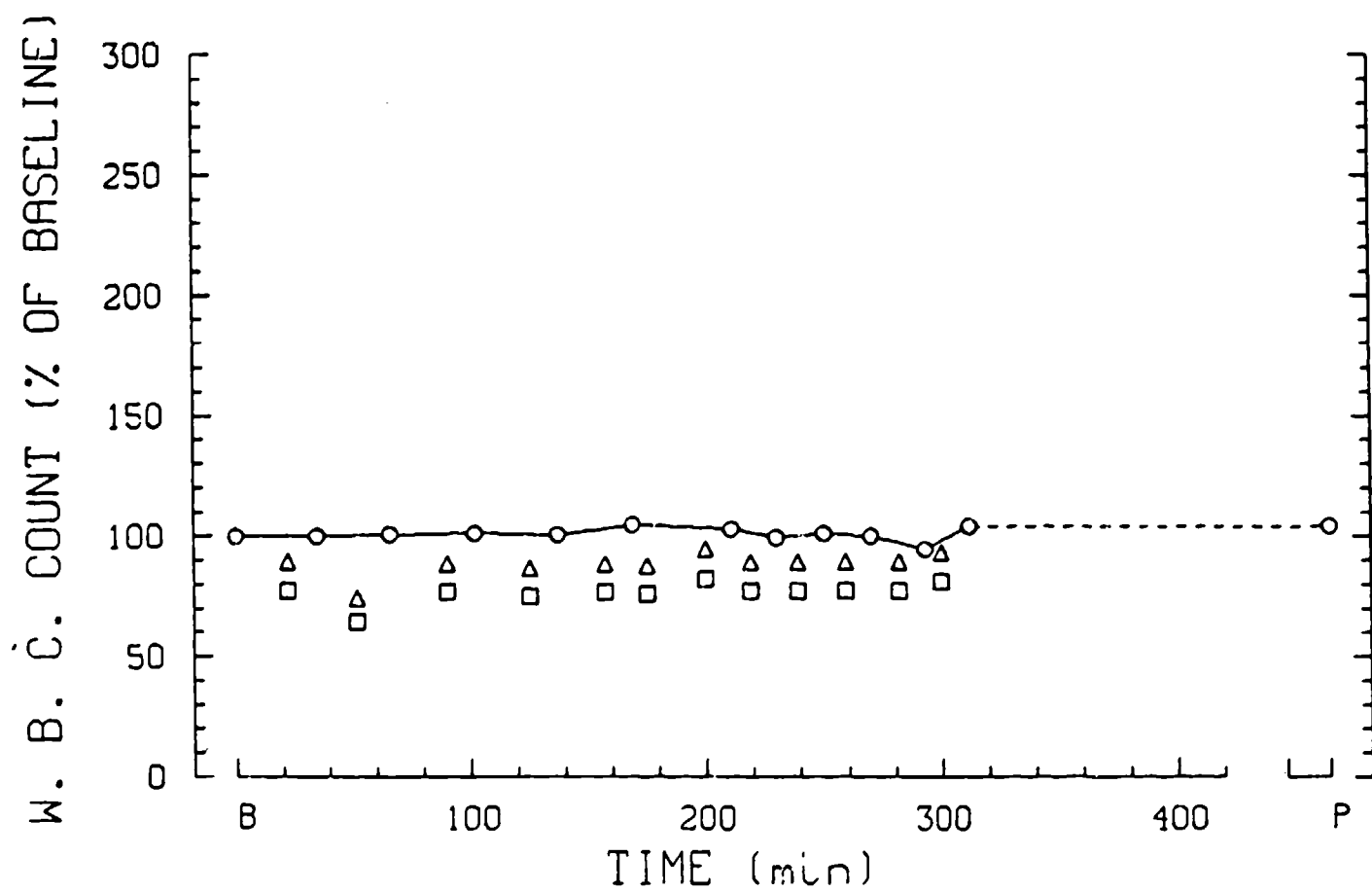
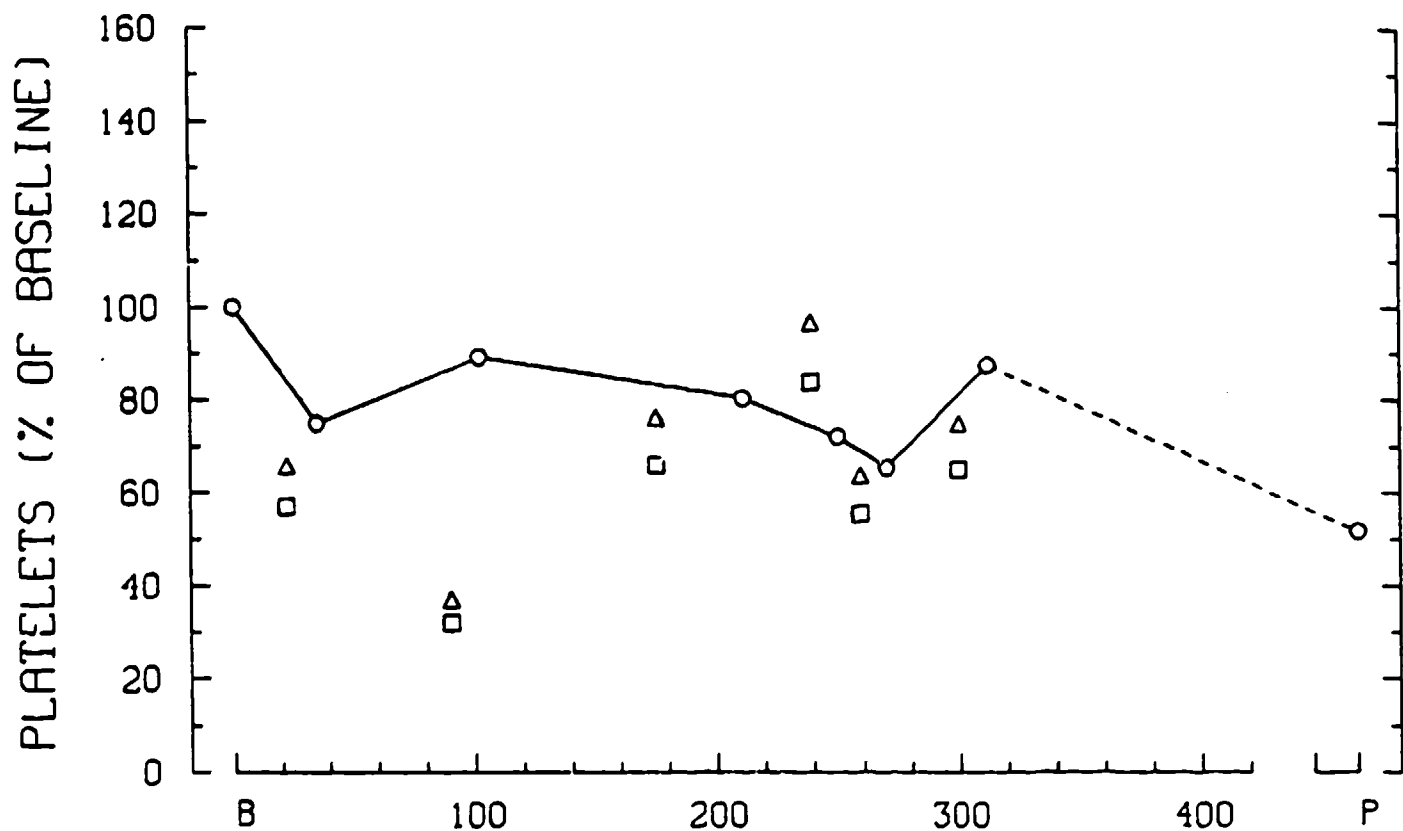


Figure A2: Control Animal A5

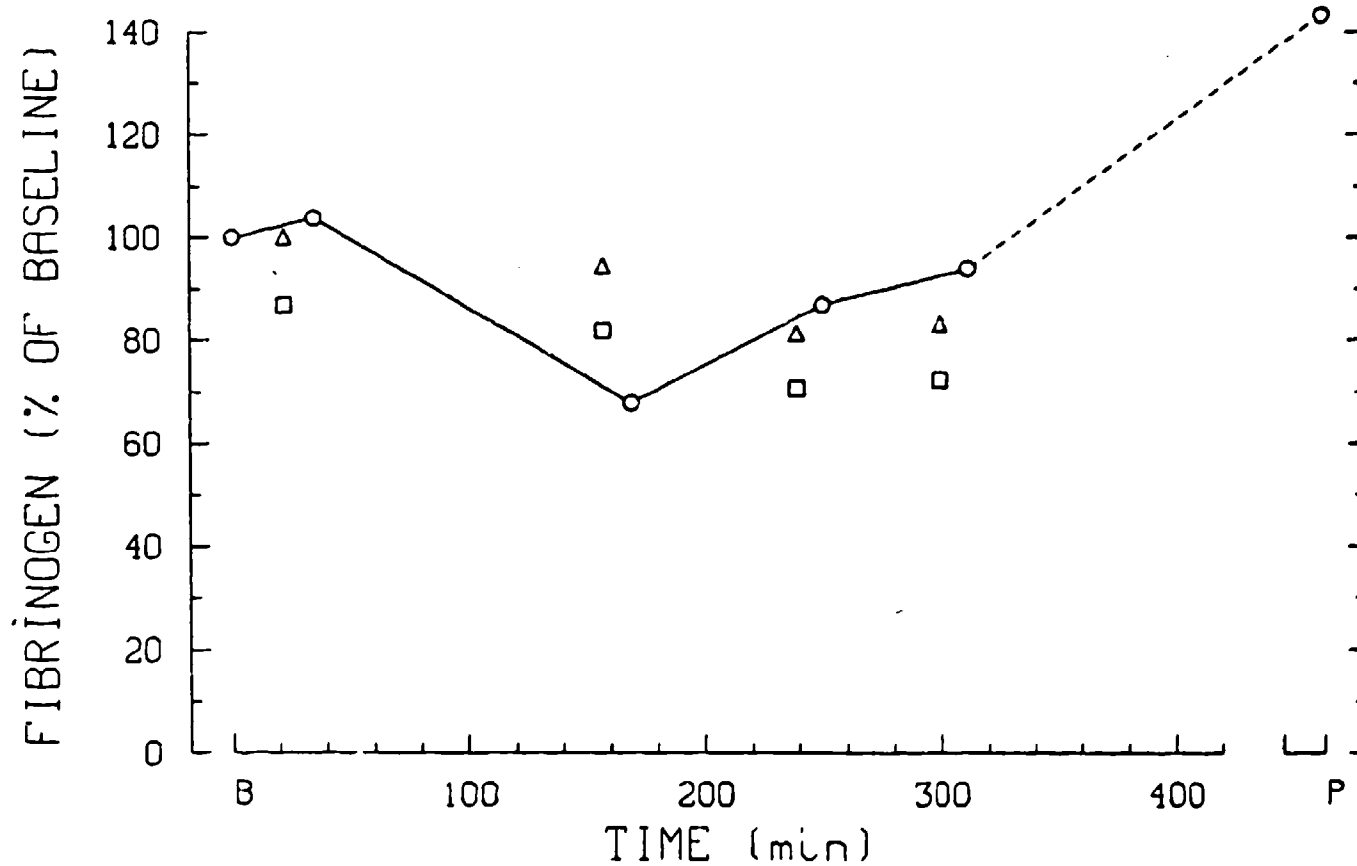
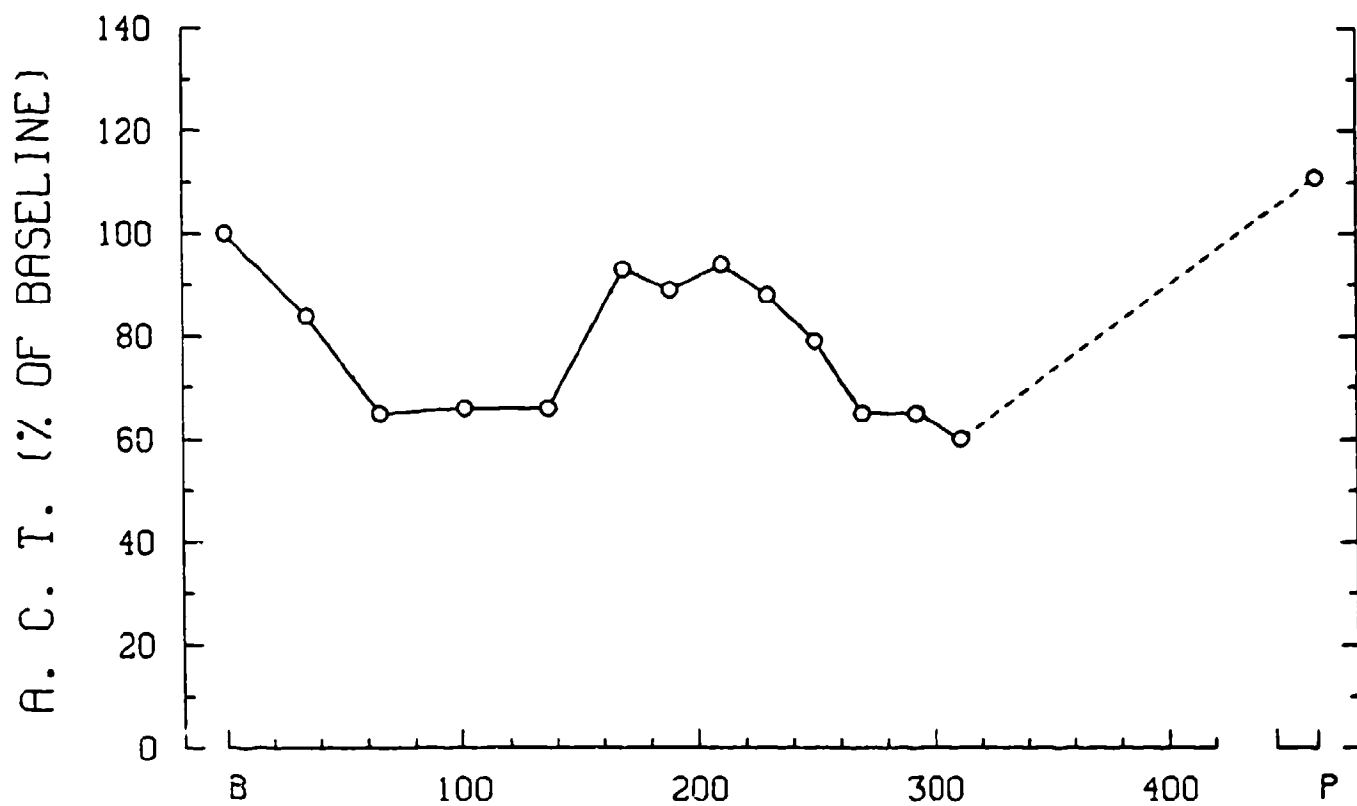


Figure A3: Control Animal A5

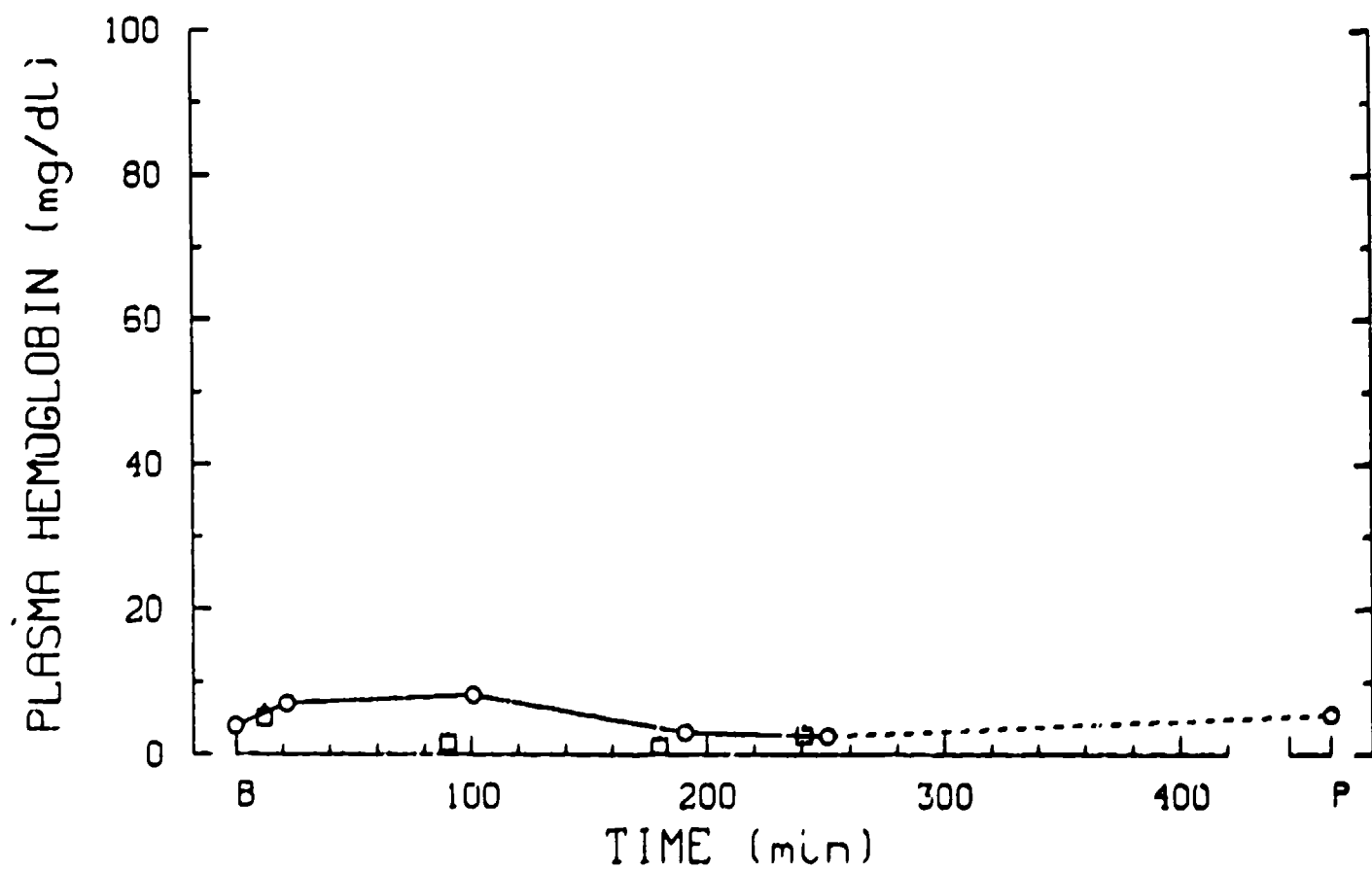
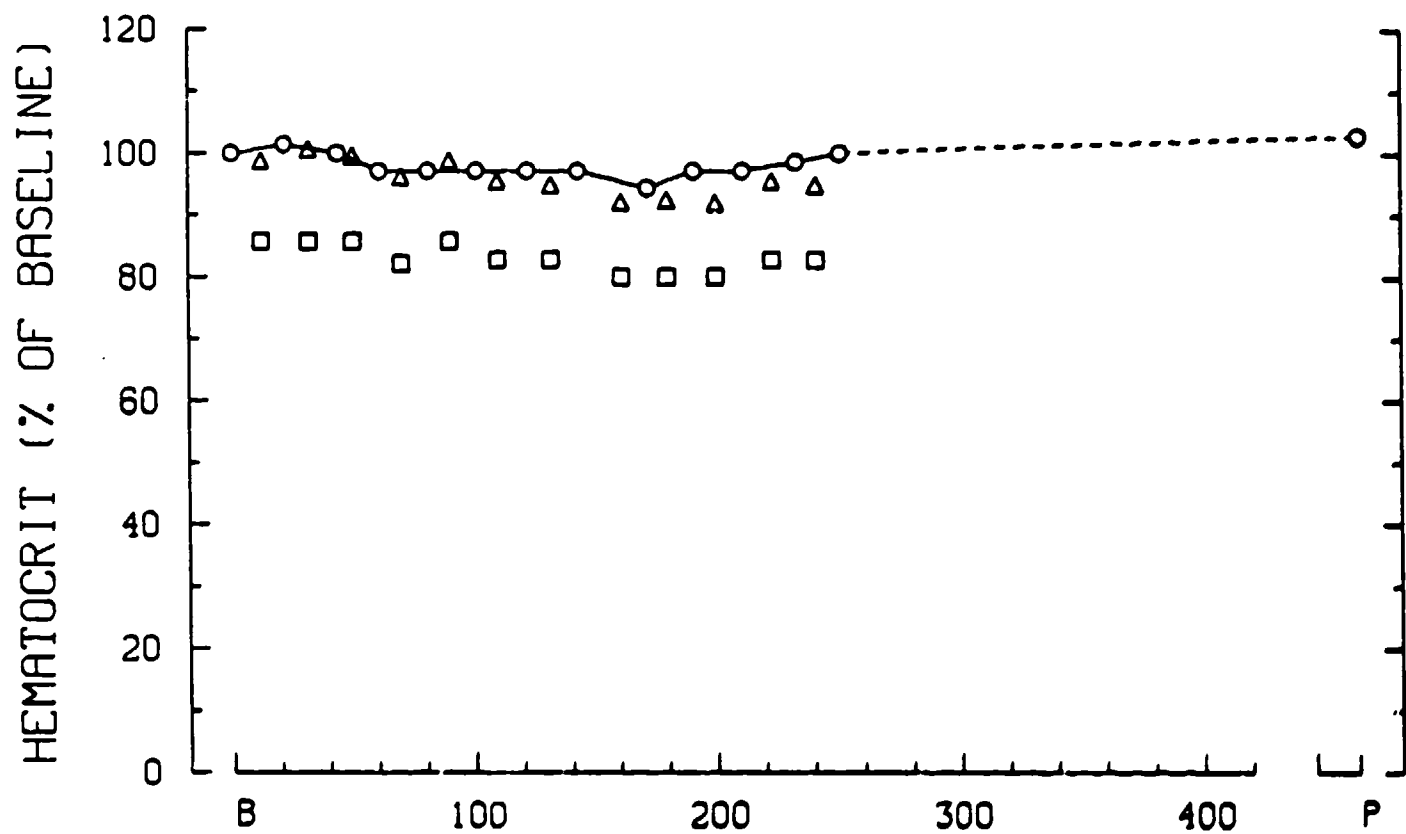


Figure A4: Control Animal A7

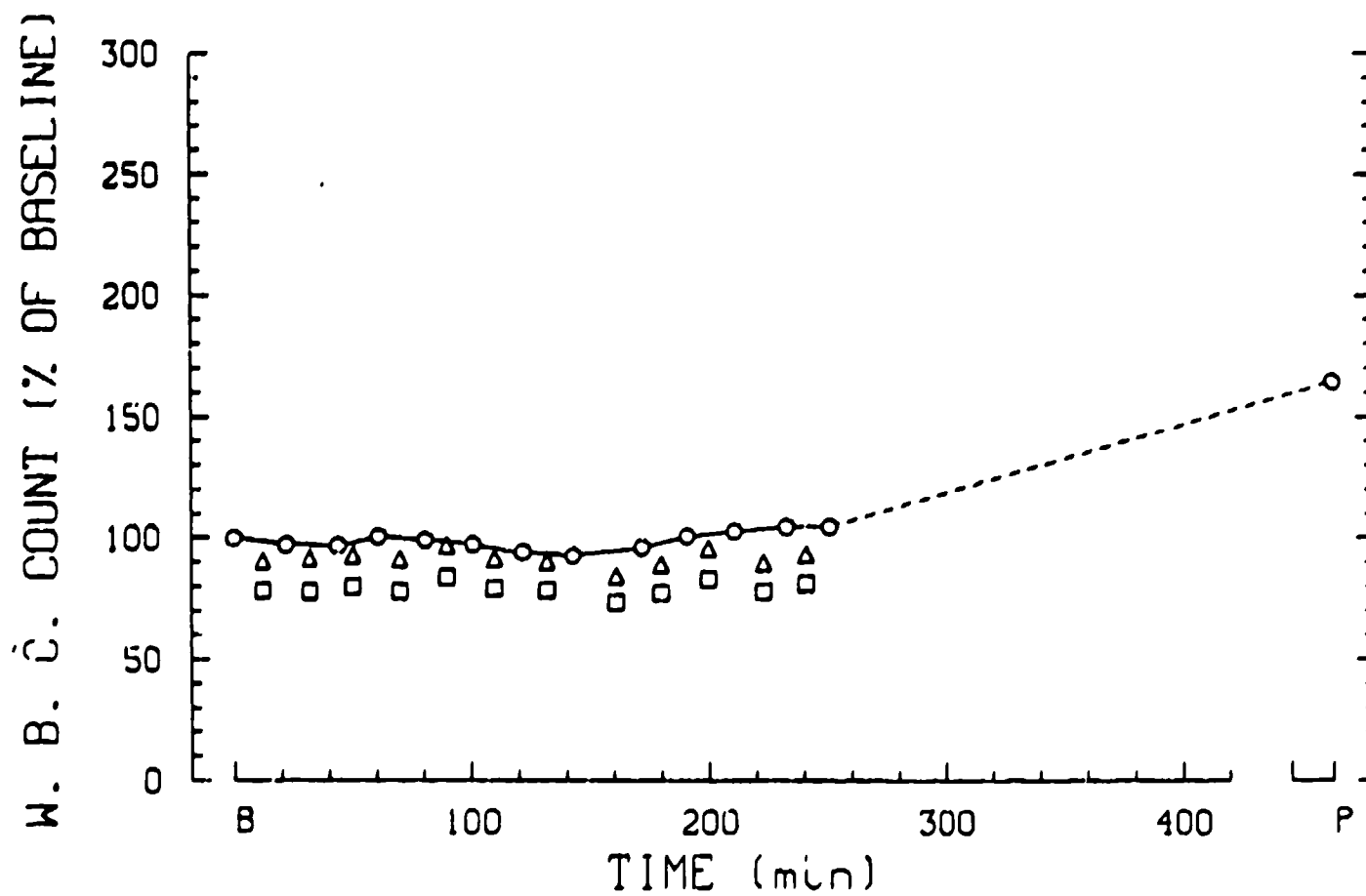
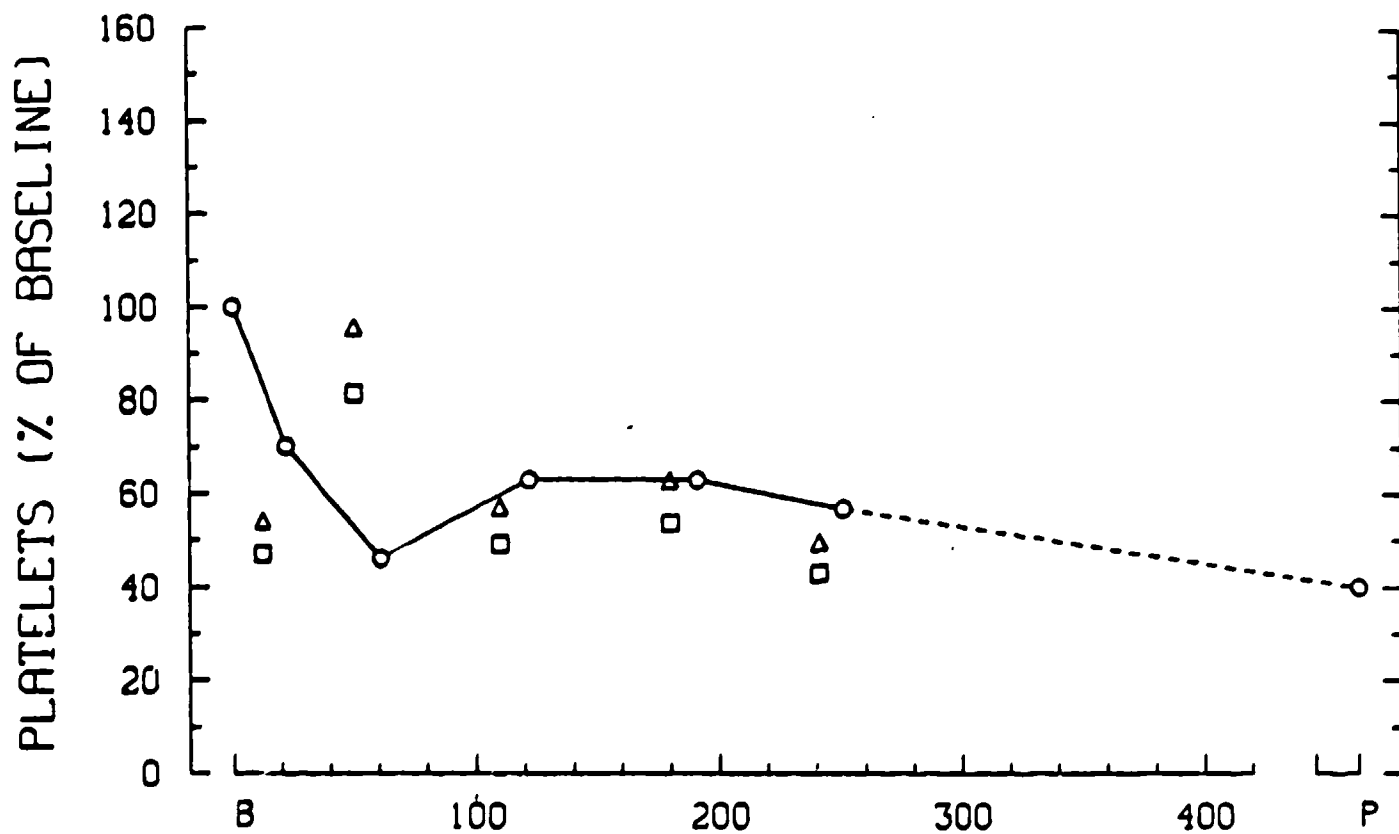


Figure A5: Control Animal A7

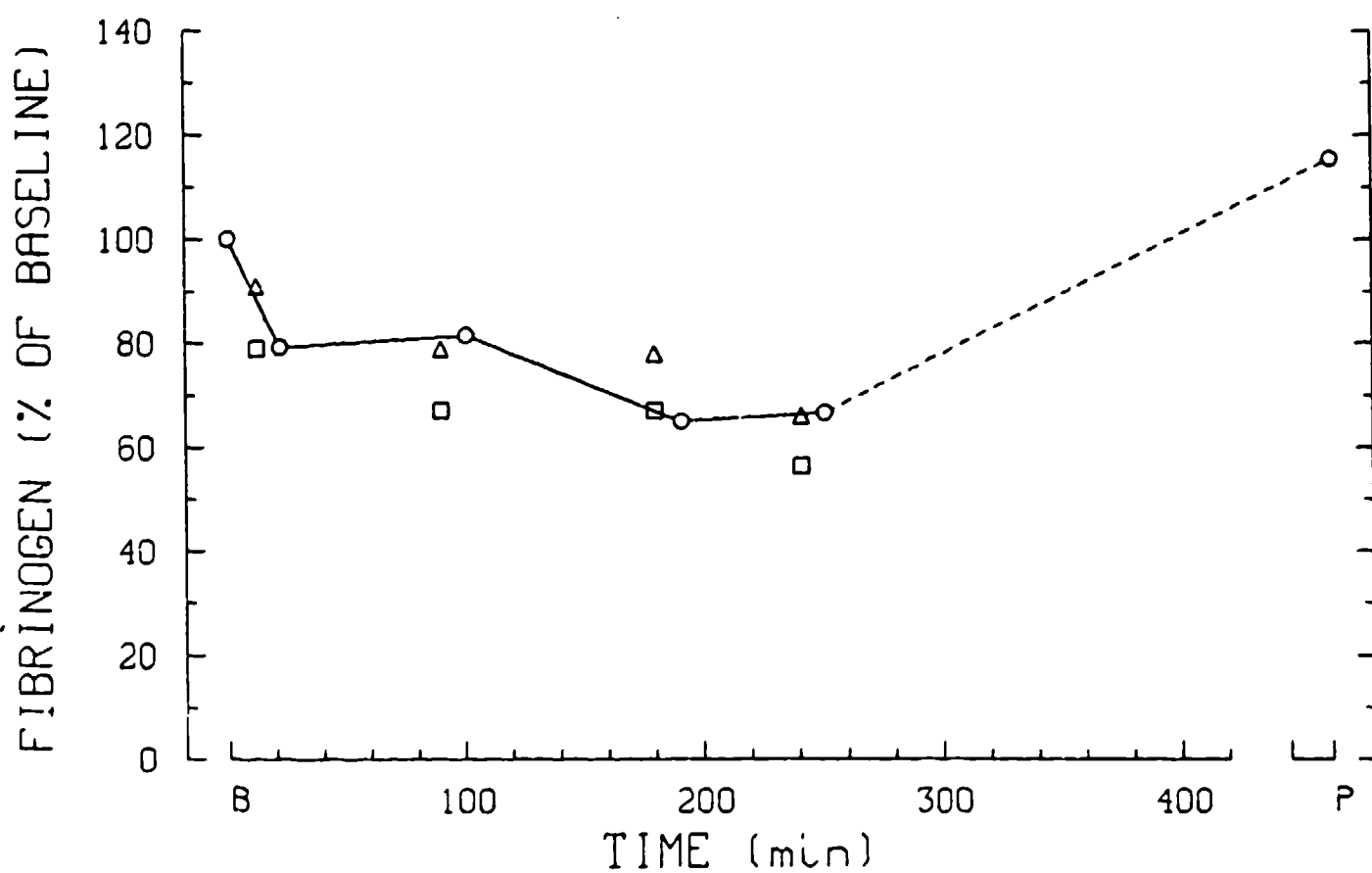
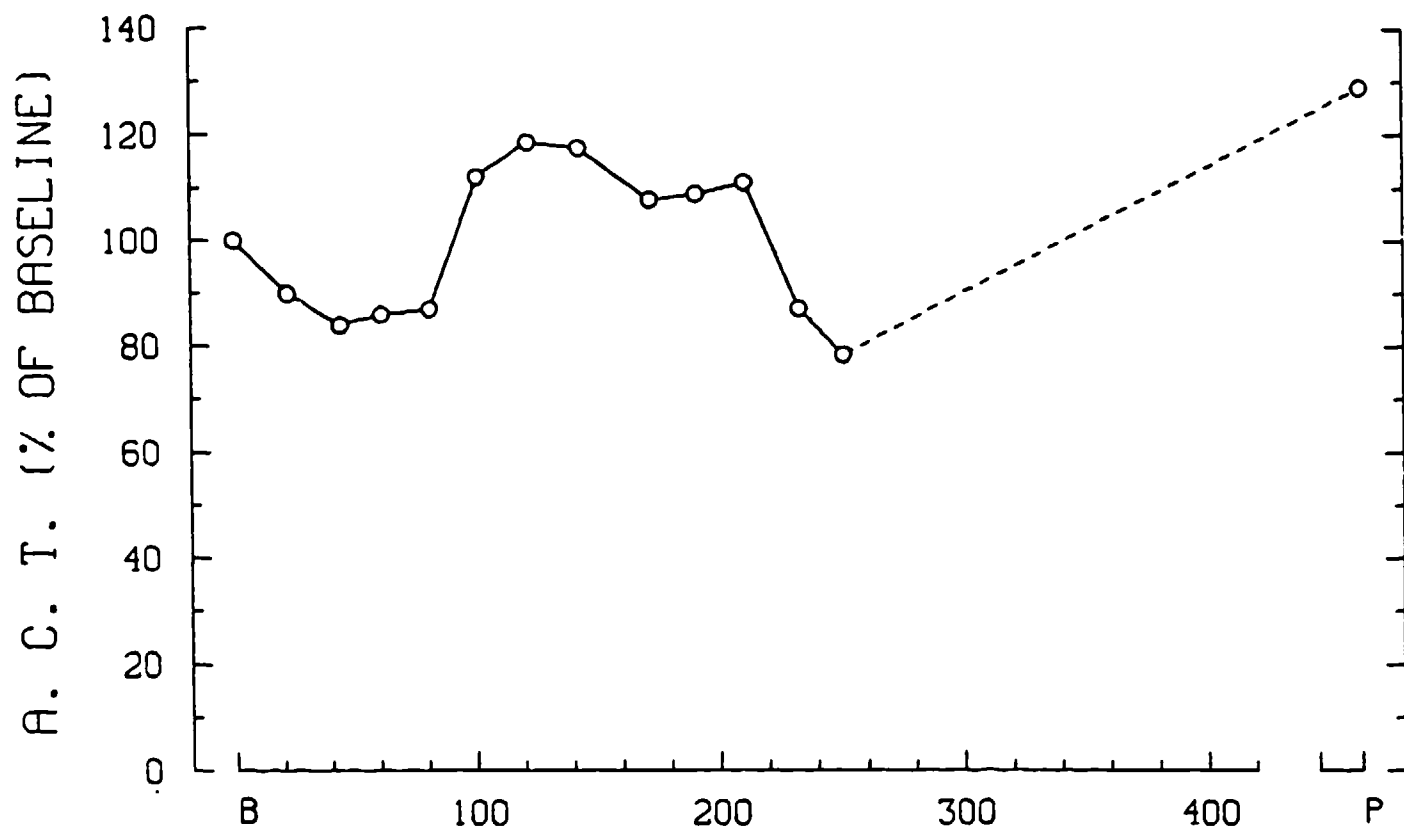


Figure A6: Control Animal A7

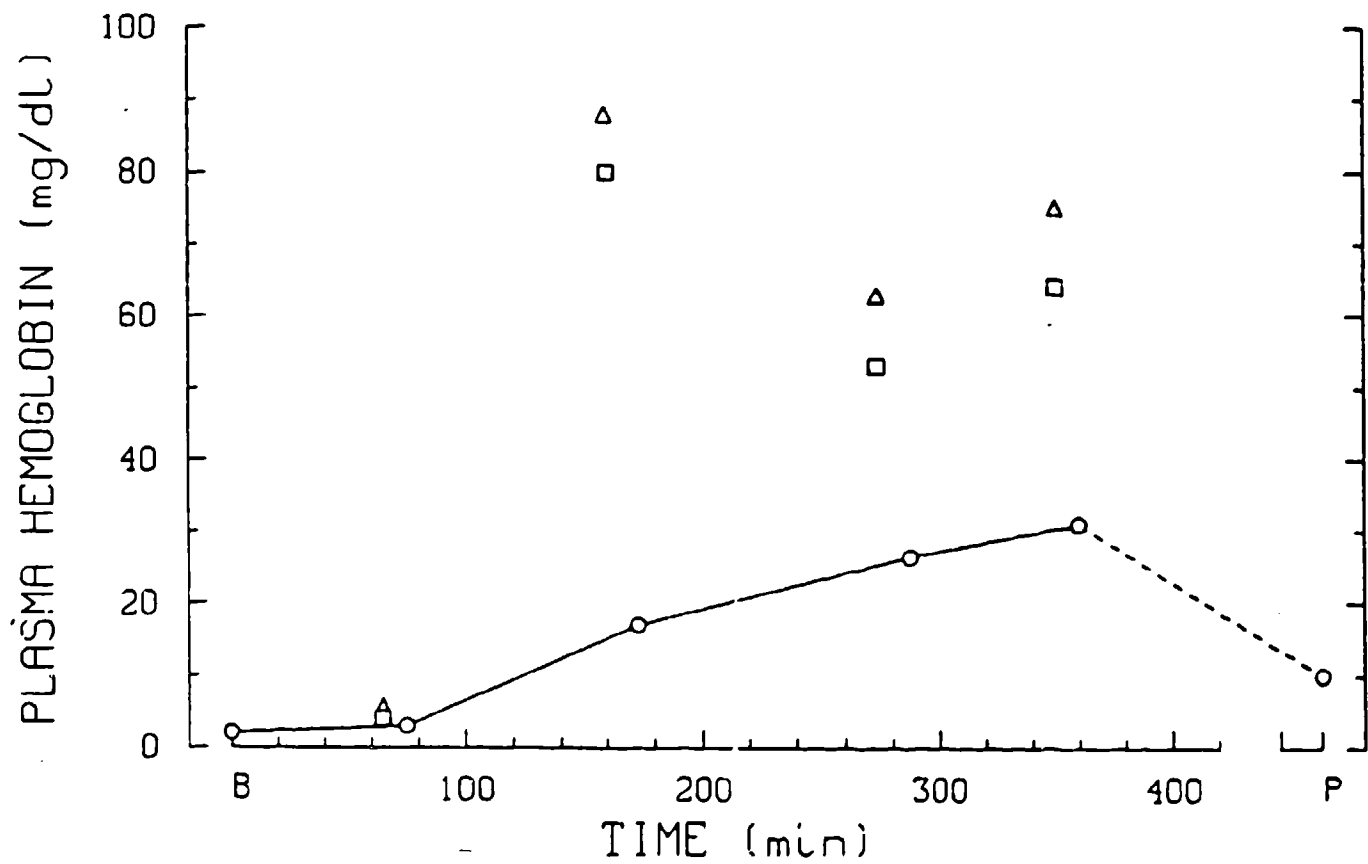
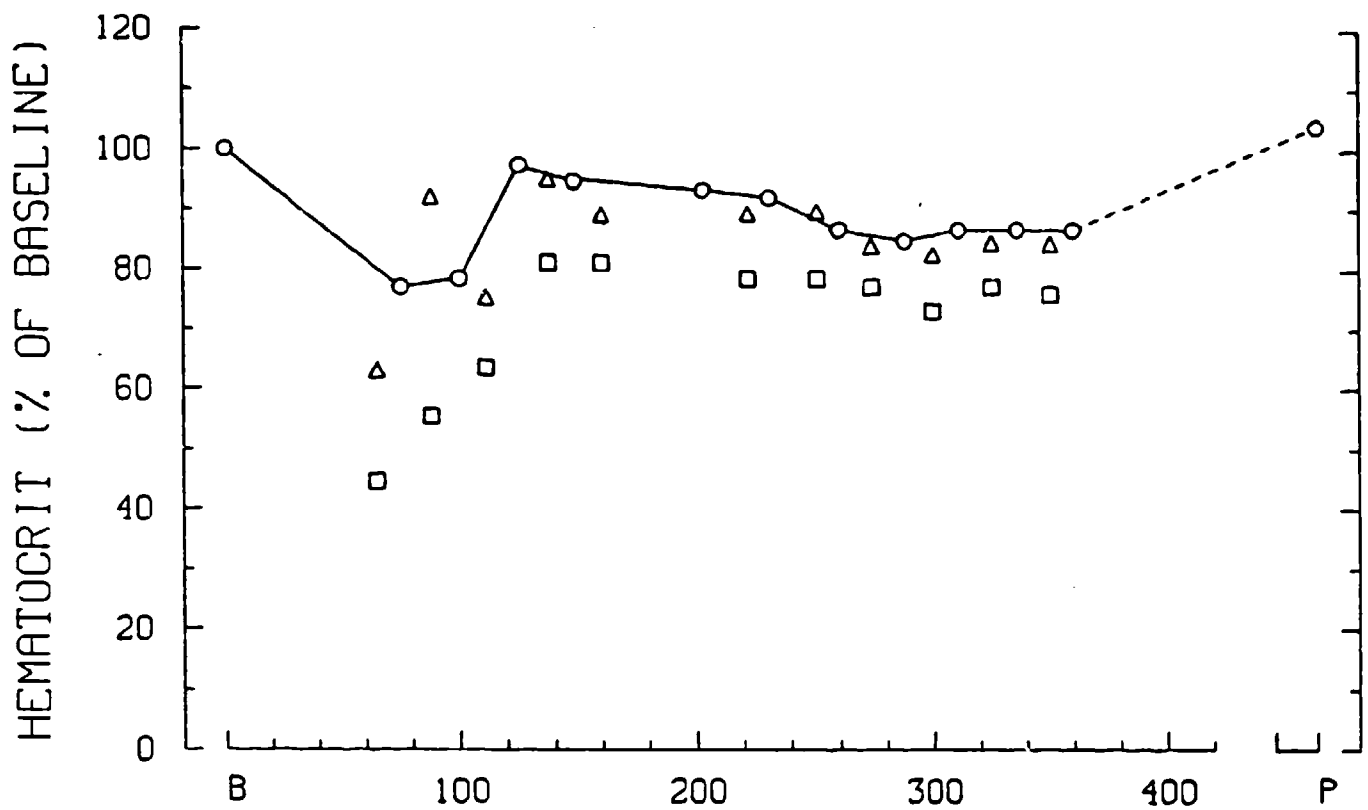


Figure A7: ATS Group Animal A4

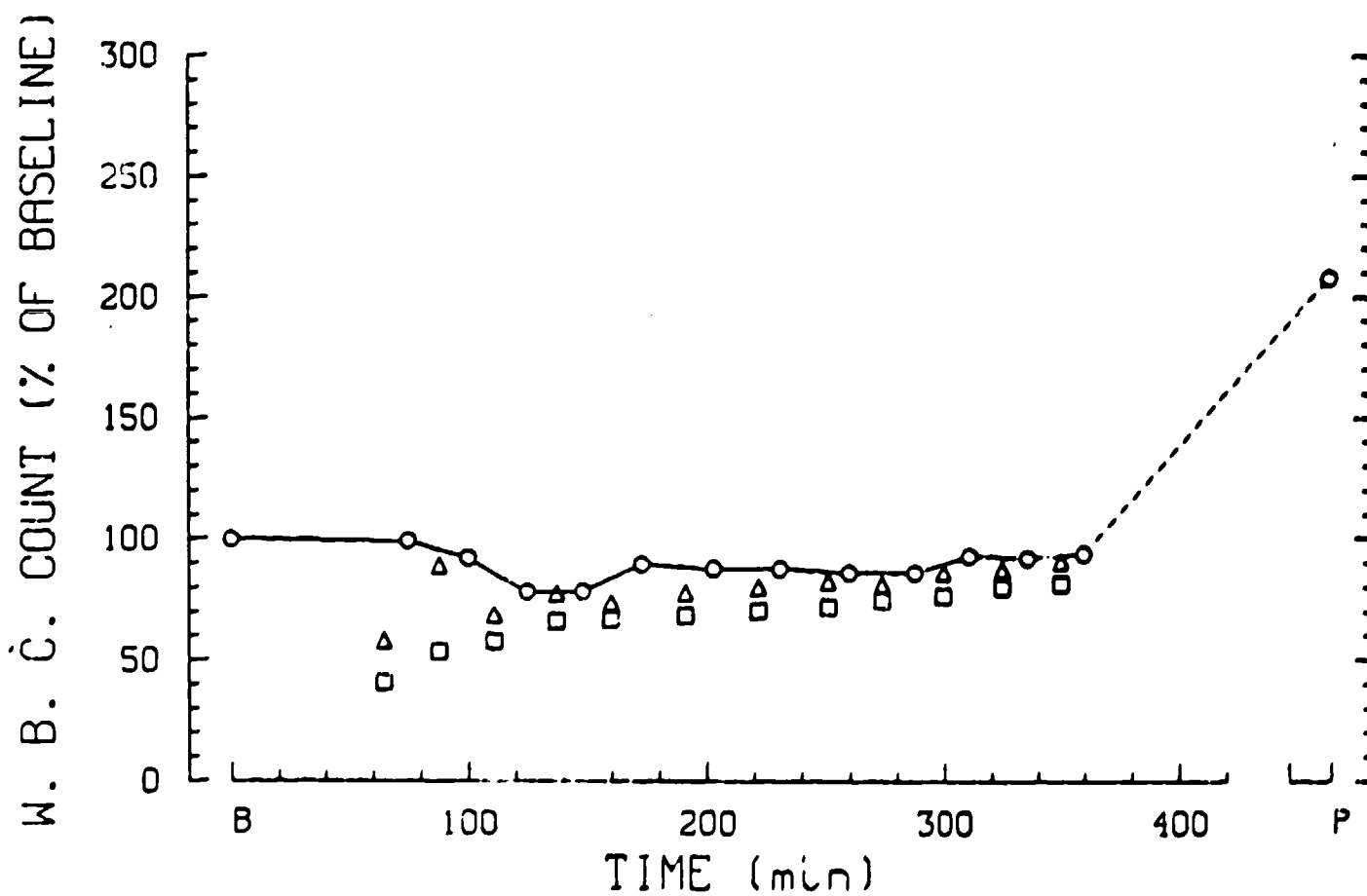
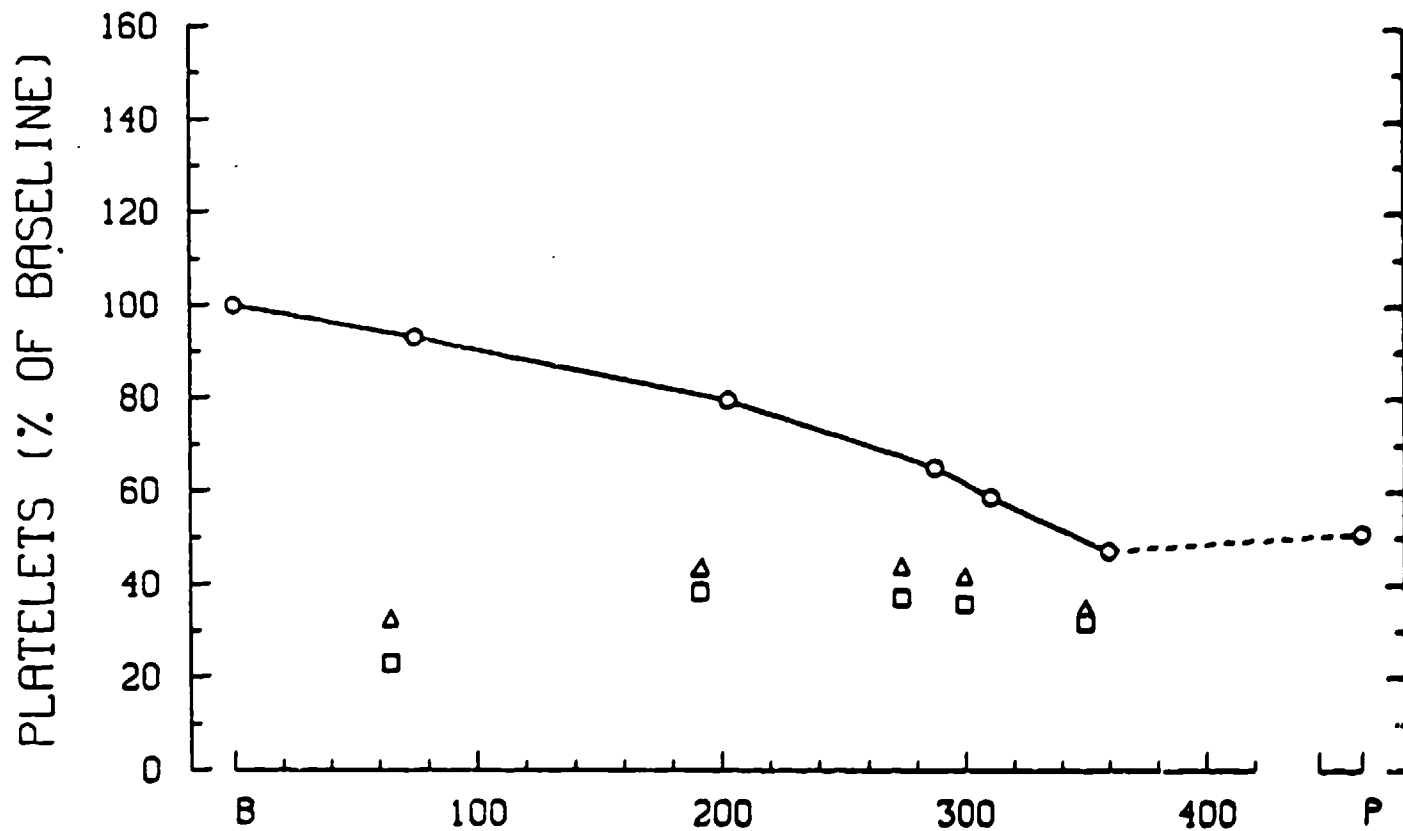


Figure A8: ATS Group Animal A4

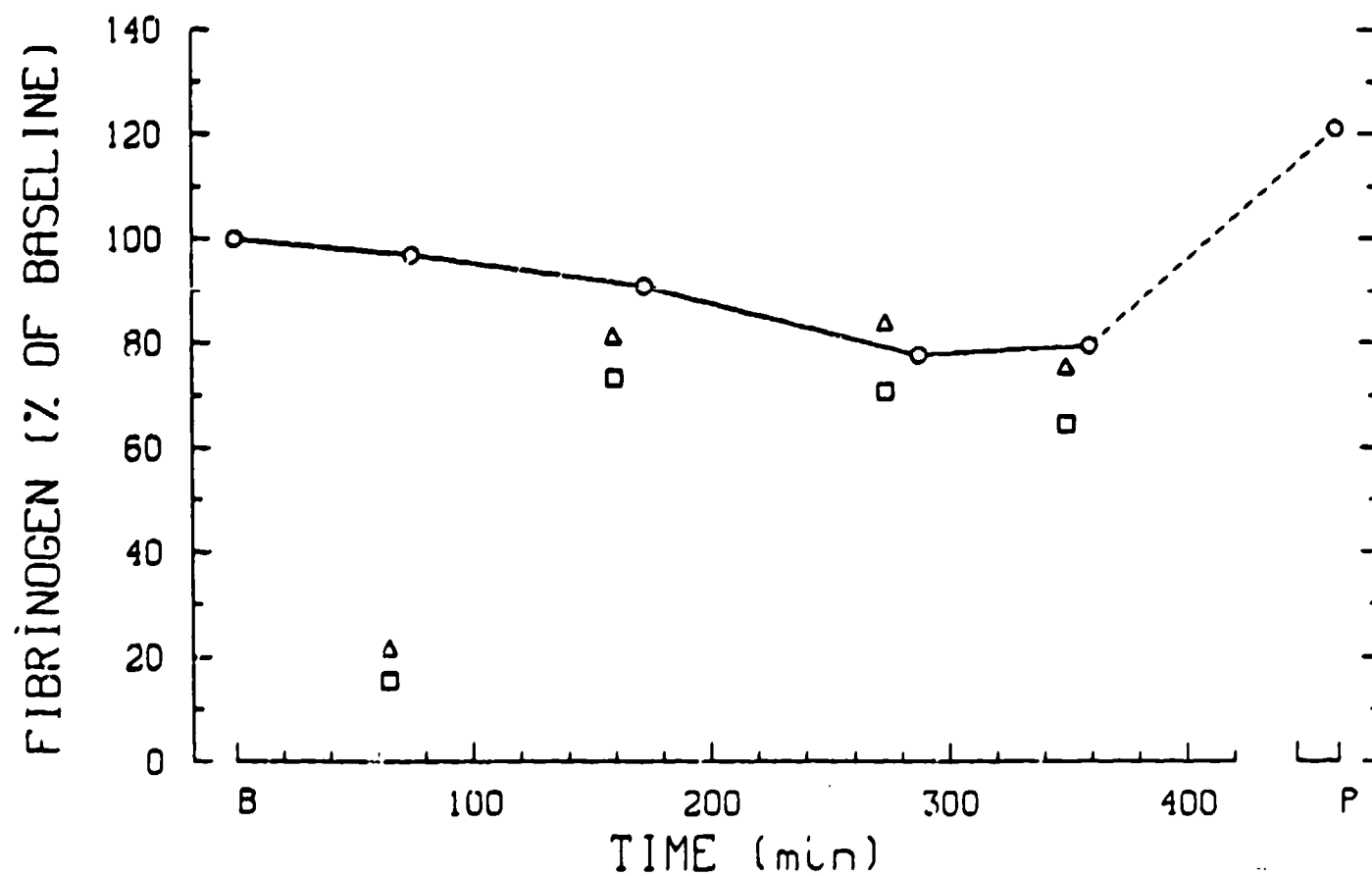
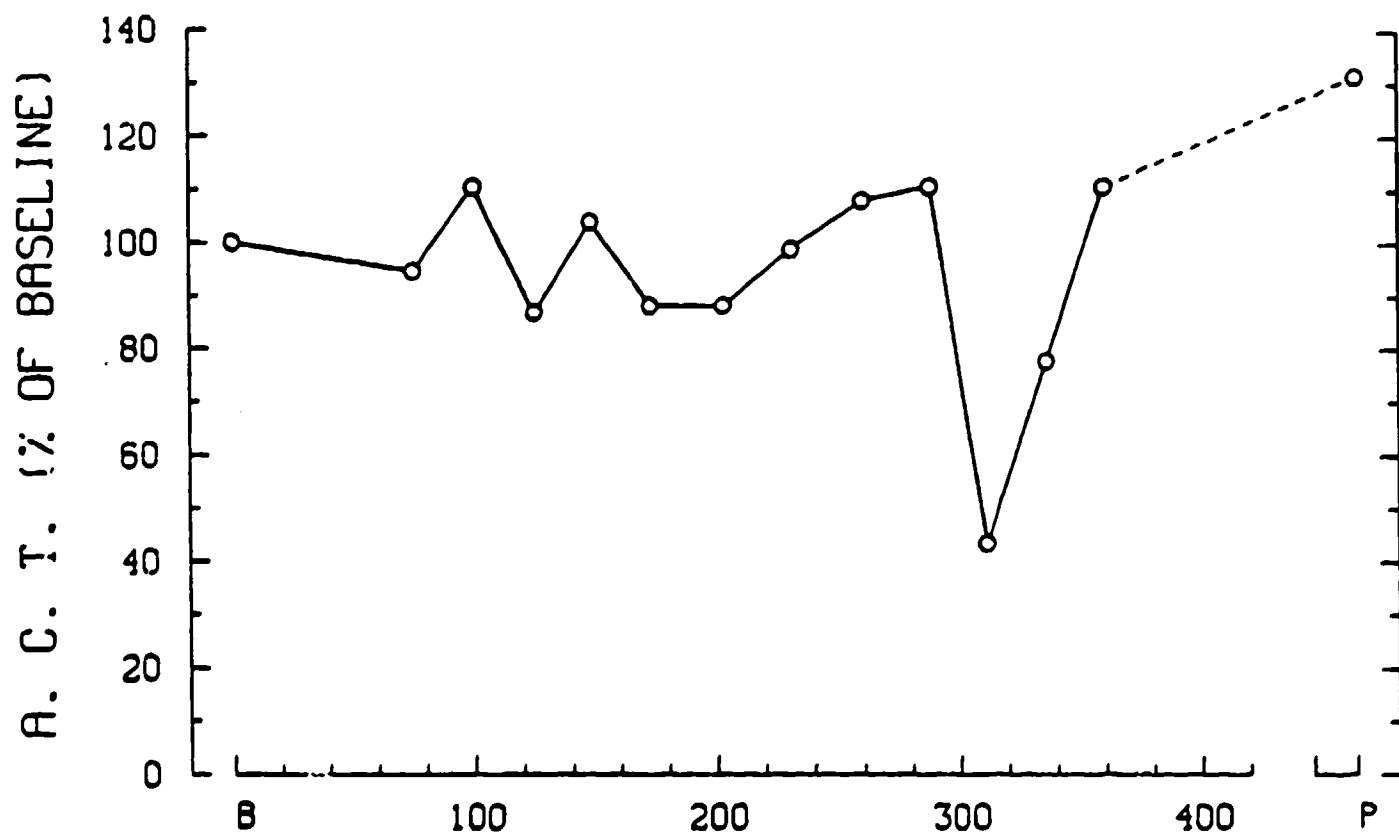


Figure A9: ATS Group Animal A4

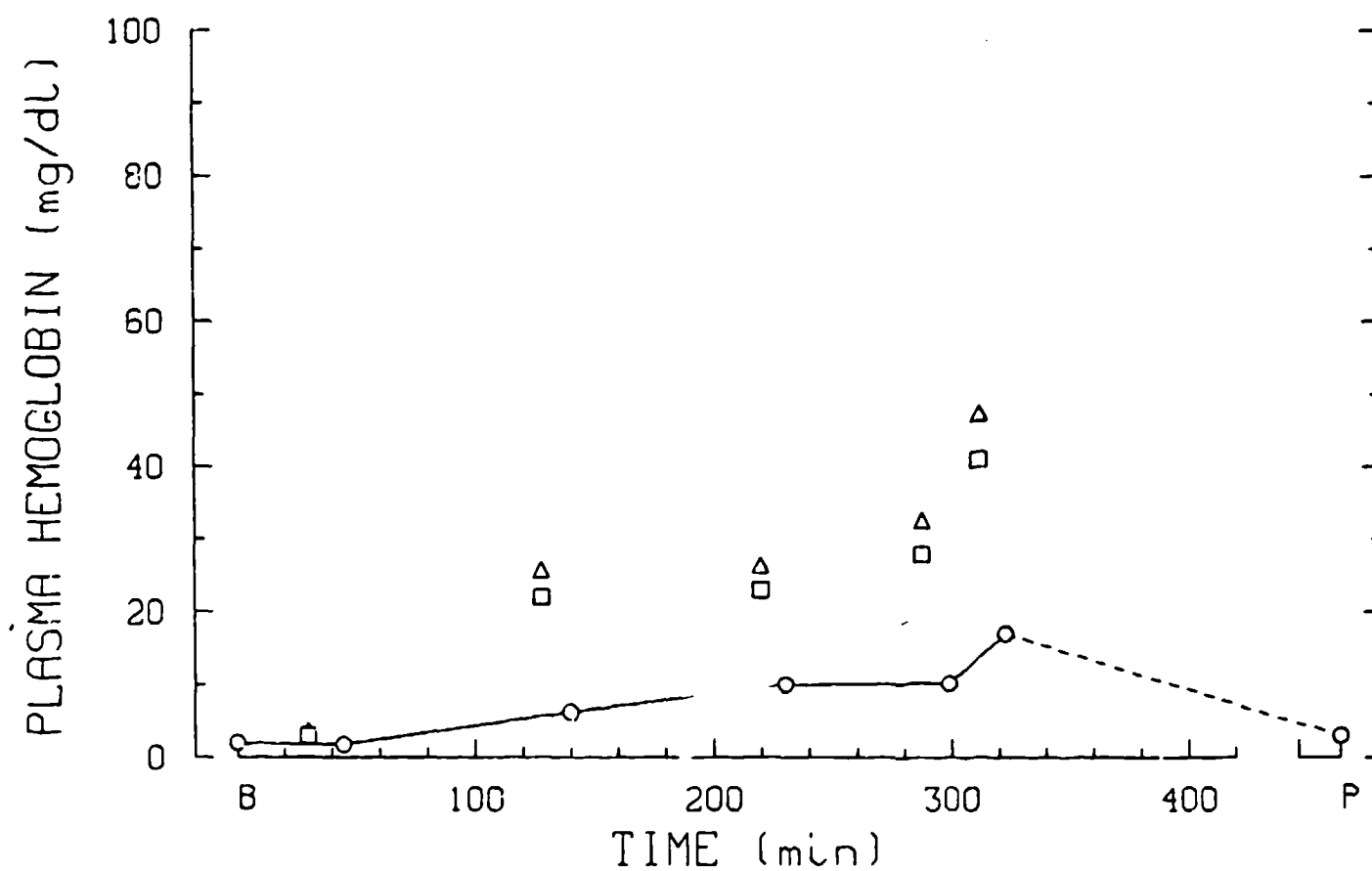
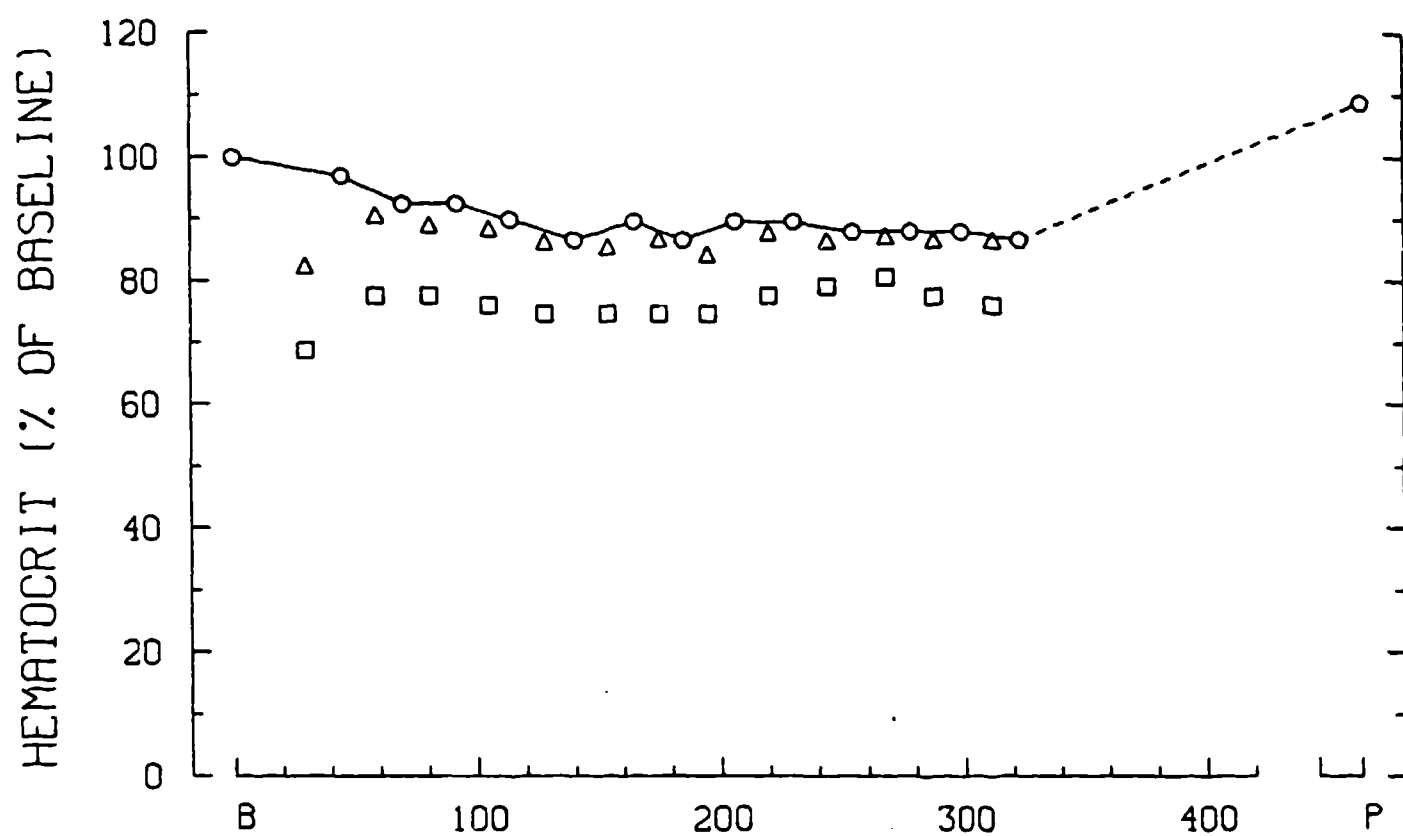


Figure A10: ATS Group Animal A6

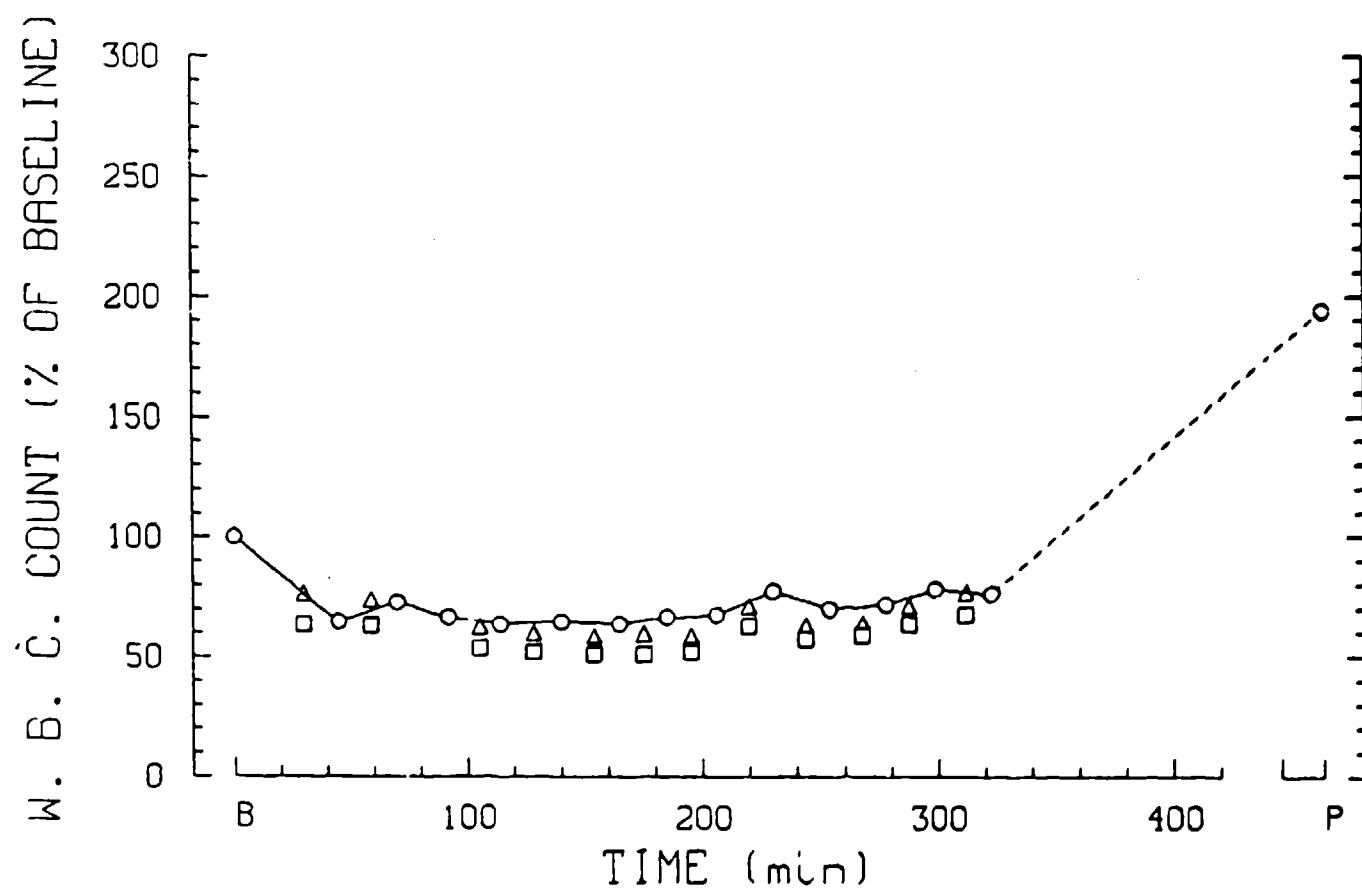
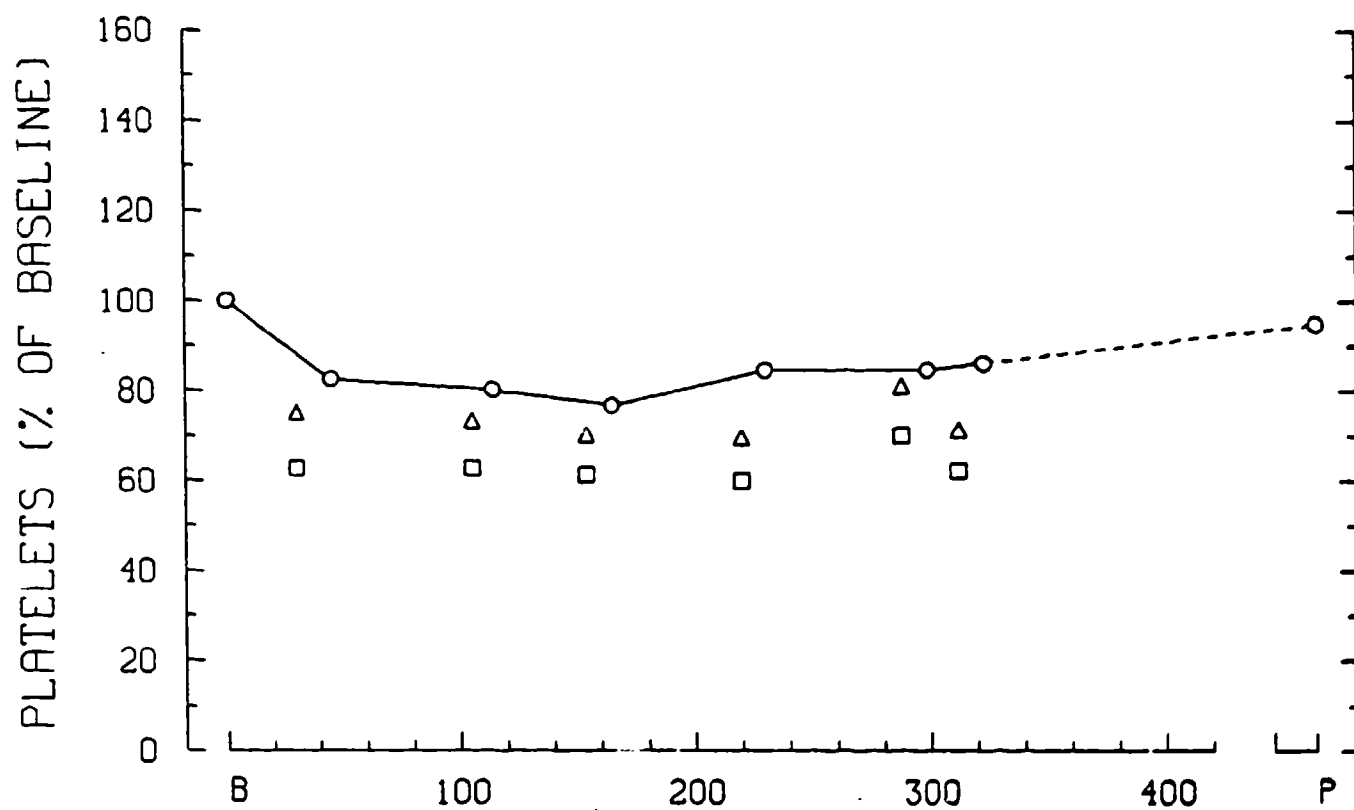


Figure A11: ATS Group Animal A6

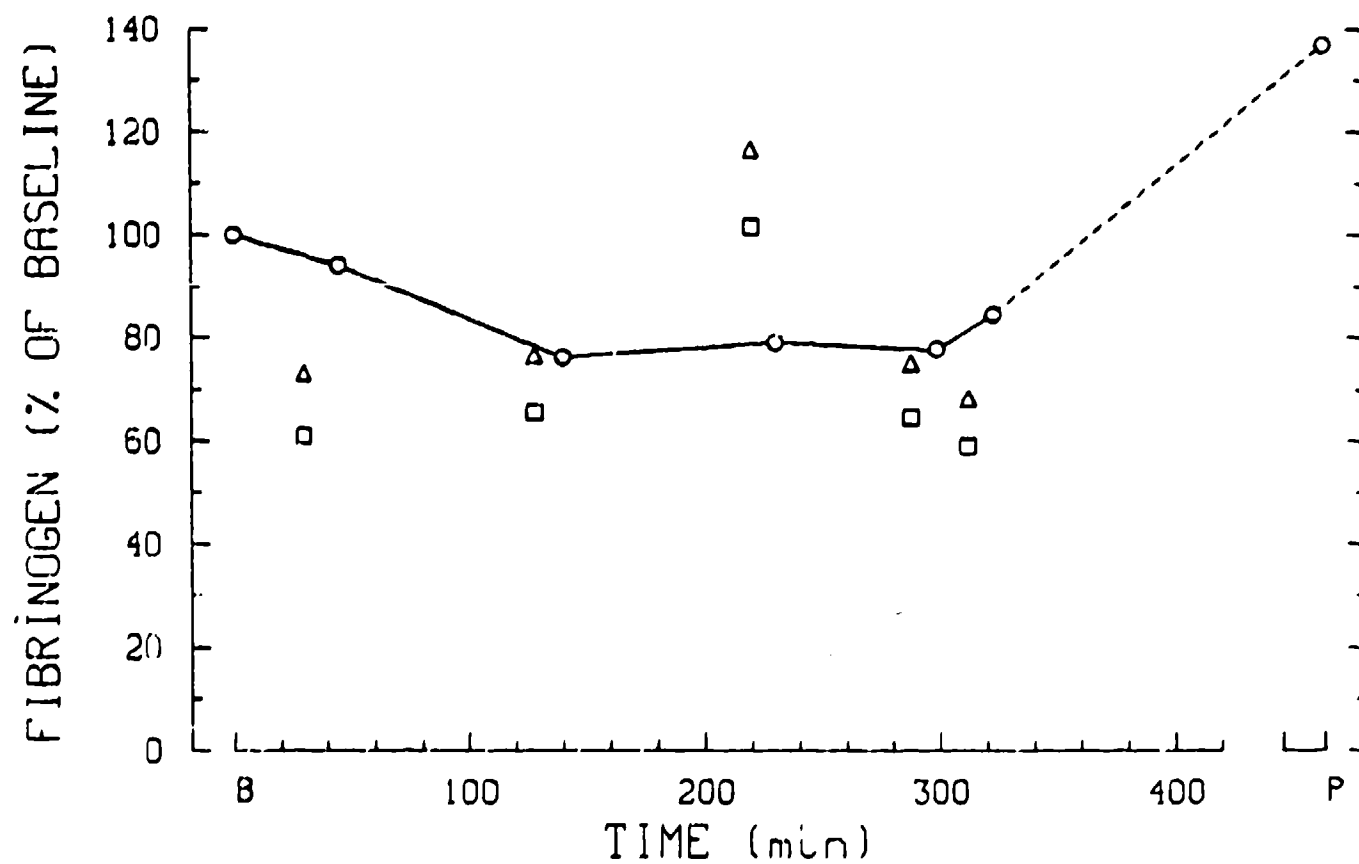
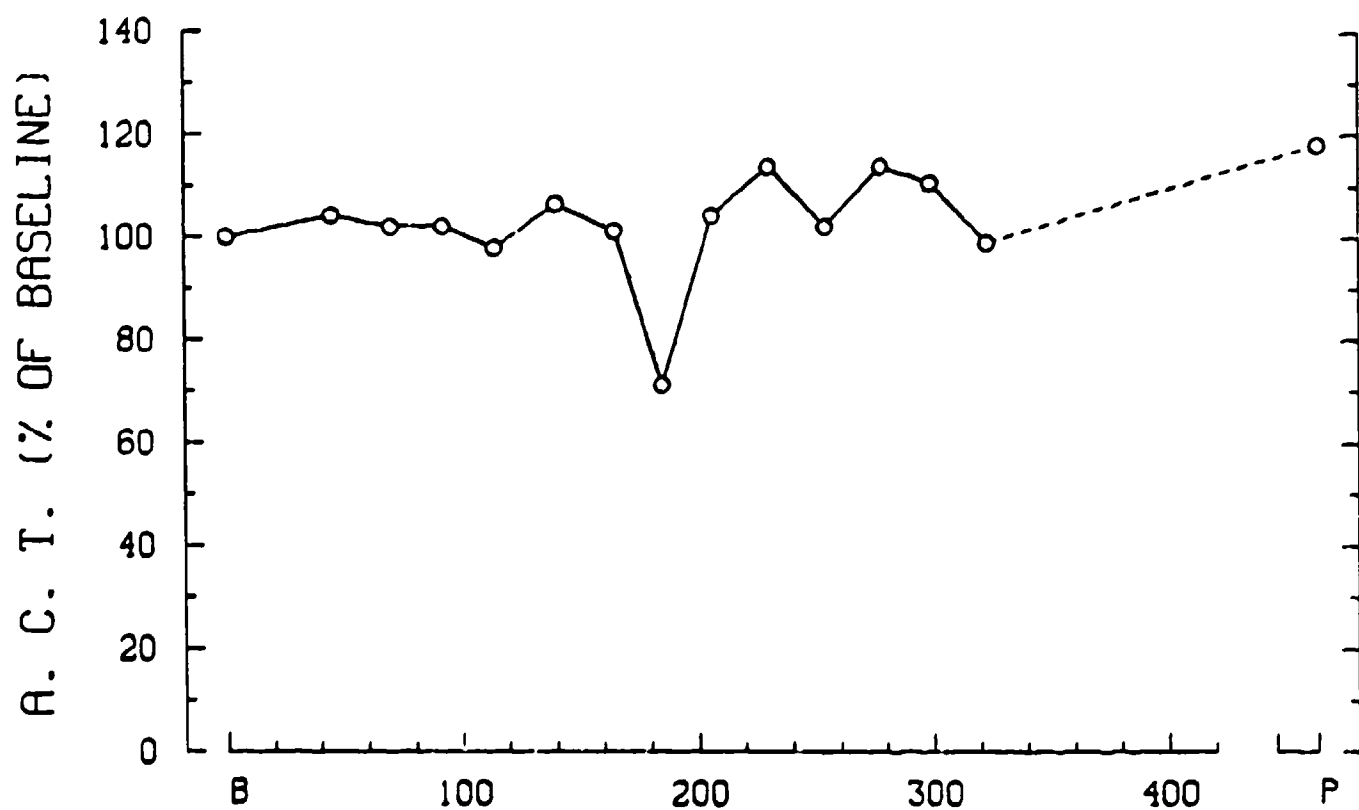


Figure A12: ATS Group Animal A6

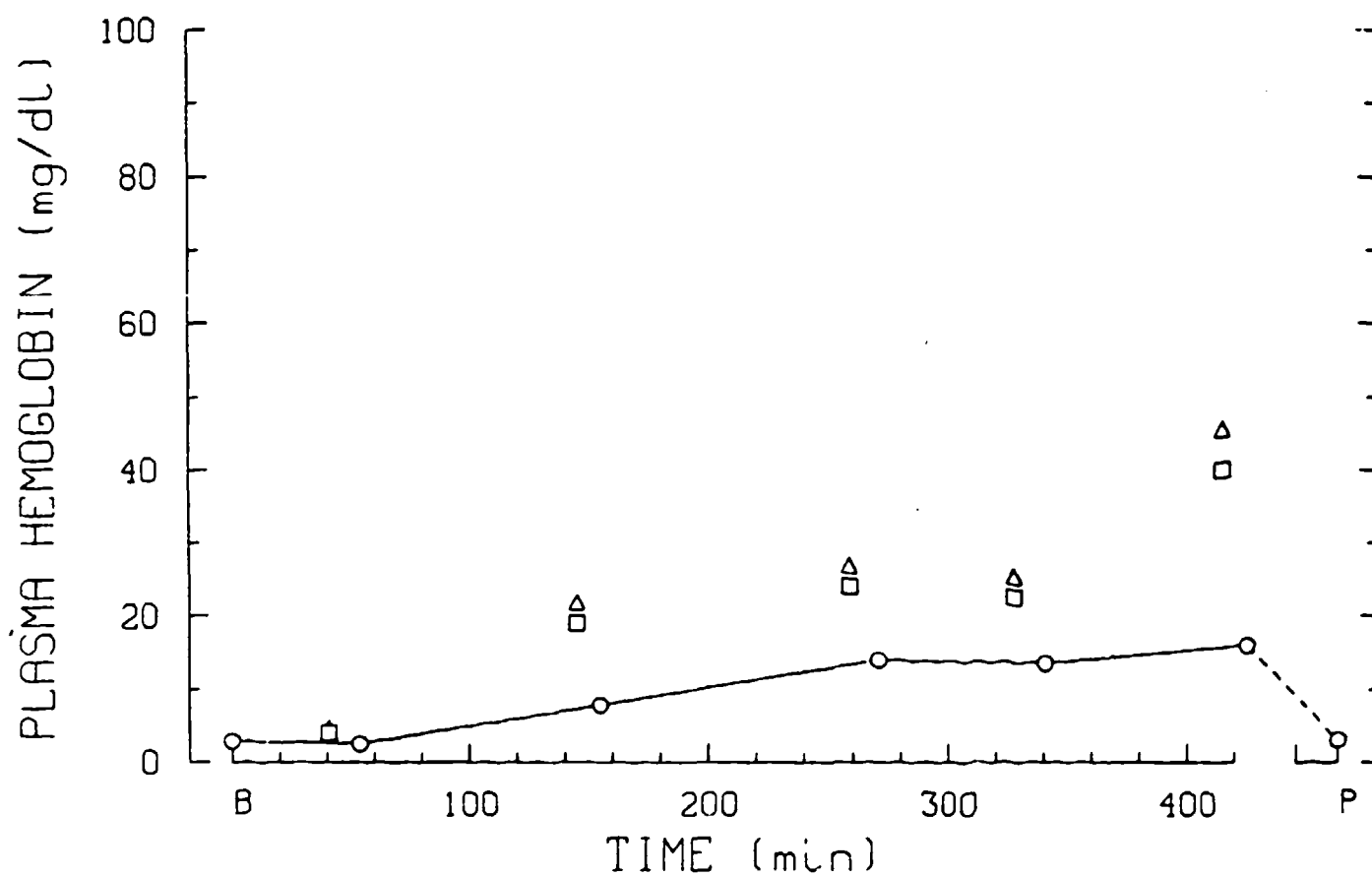
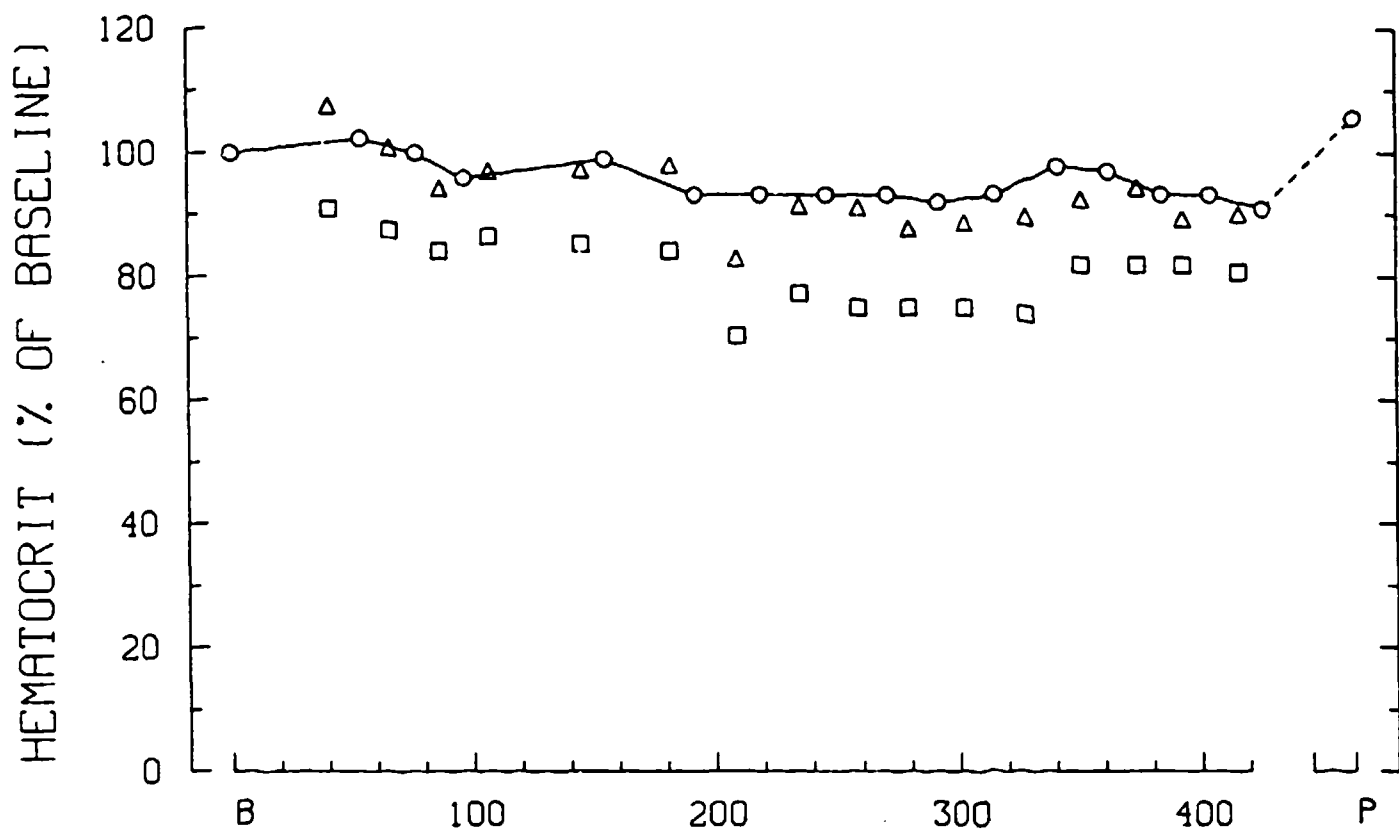


Figure A13: ATS Group Animal A9

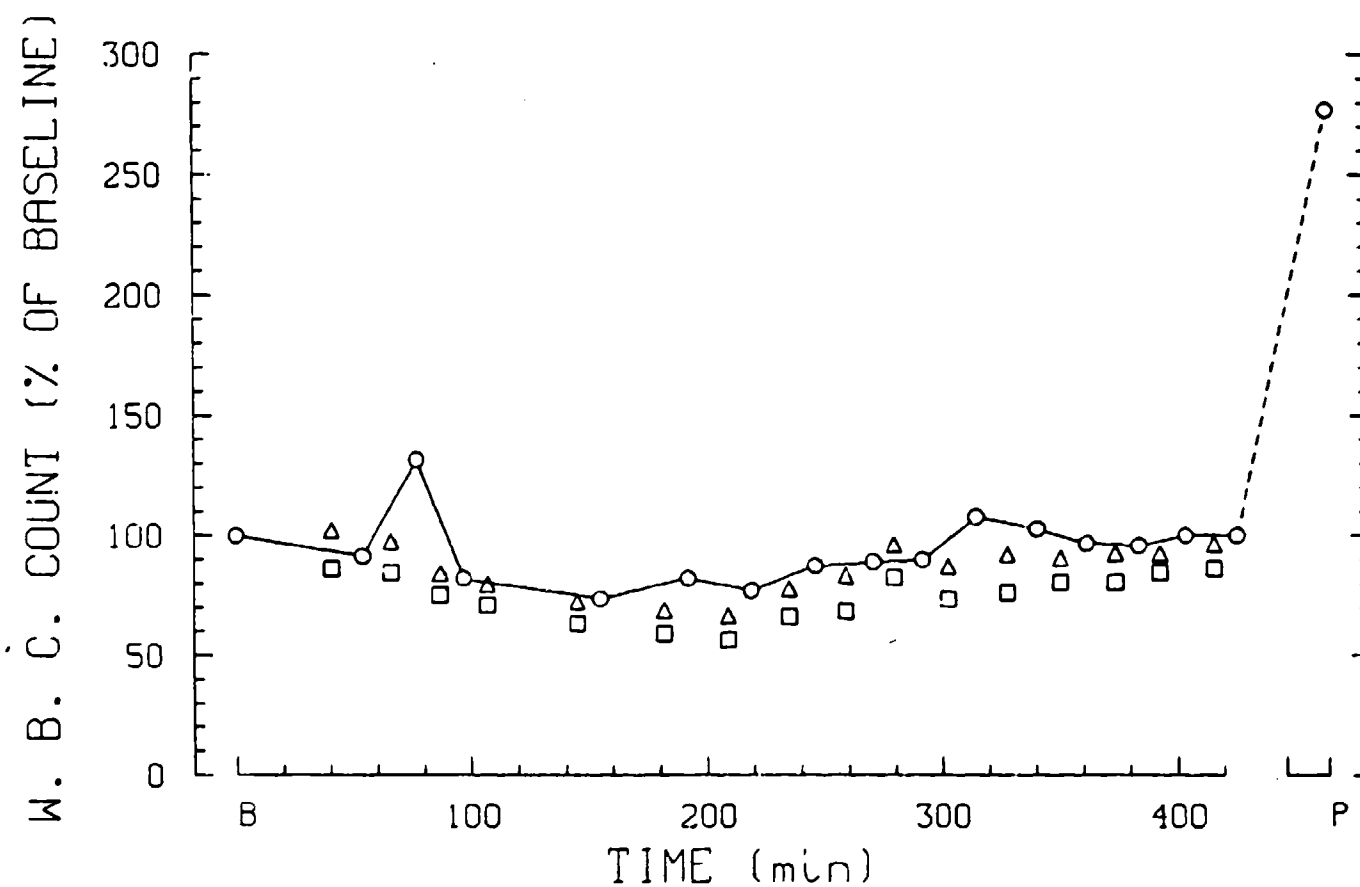
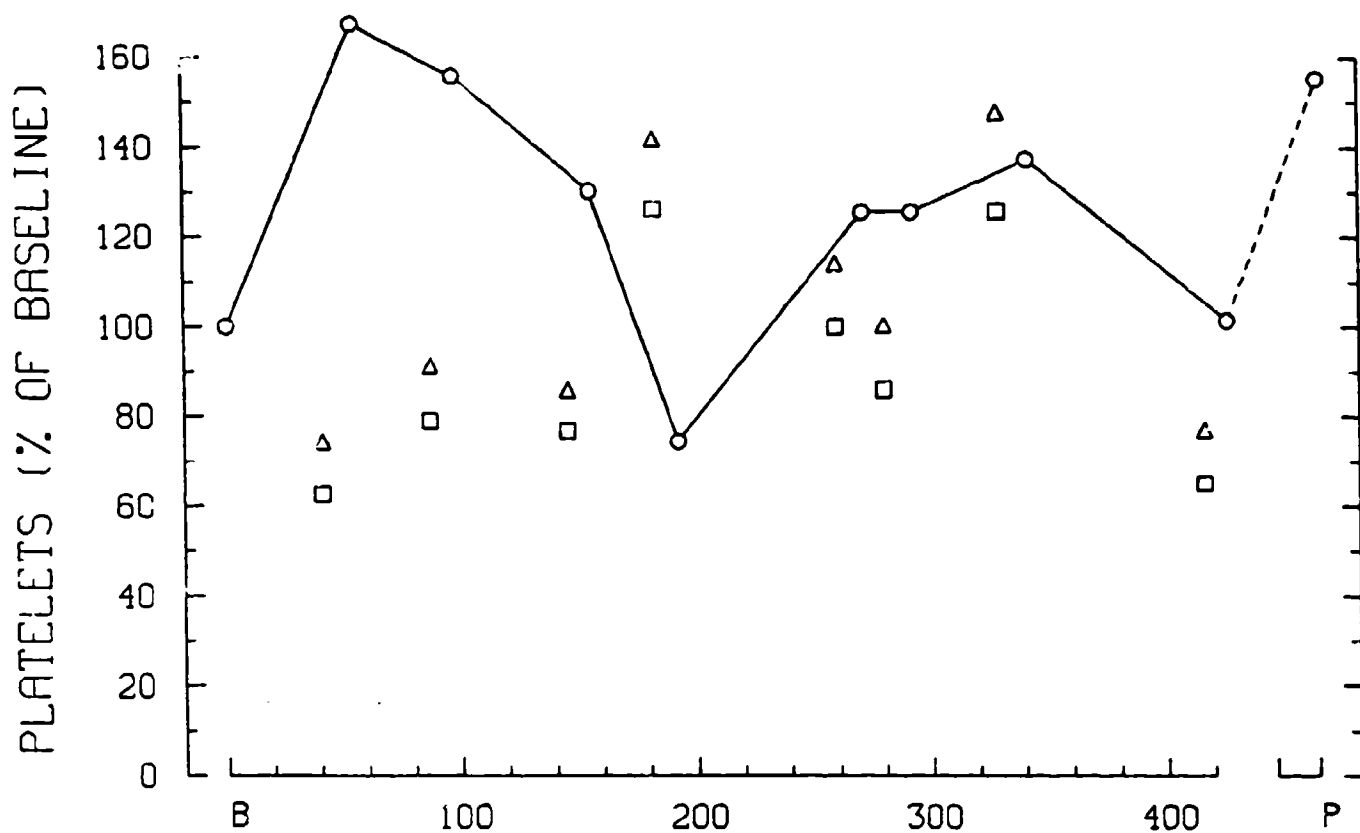


Figure A14: ATS Group Animal A9

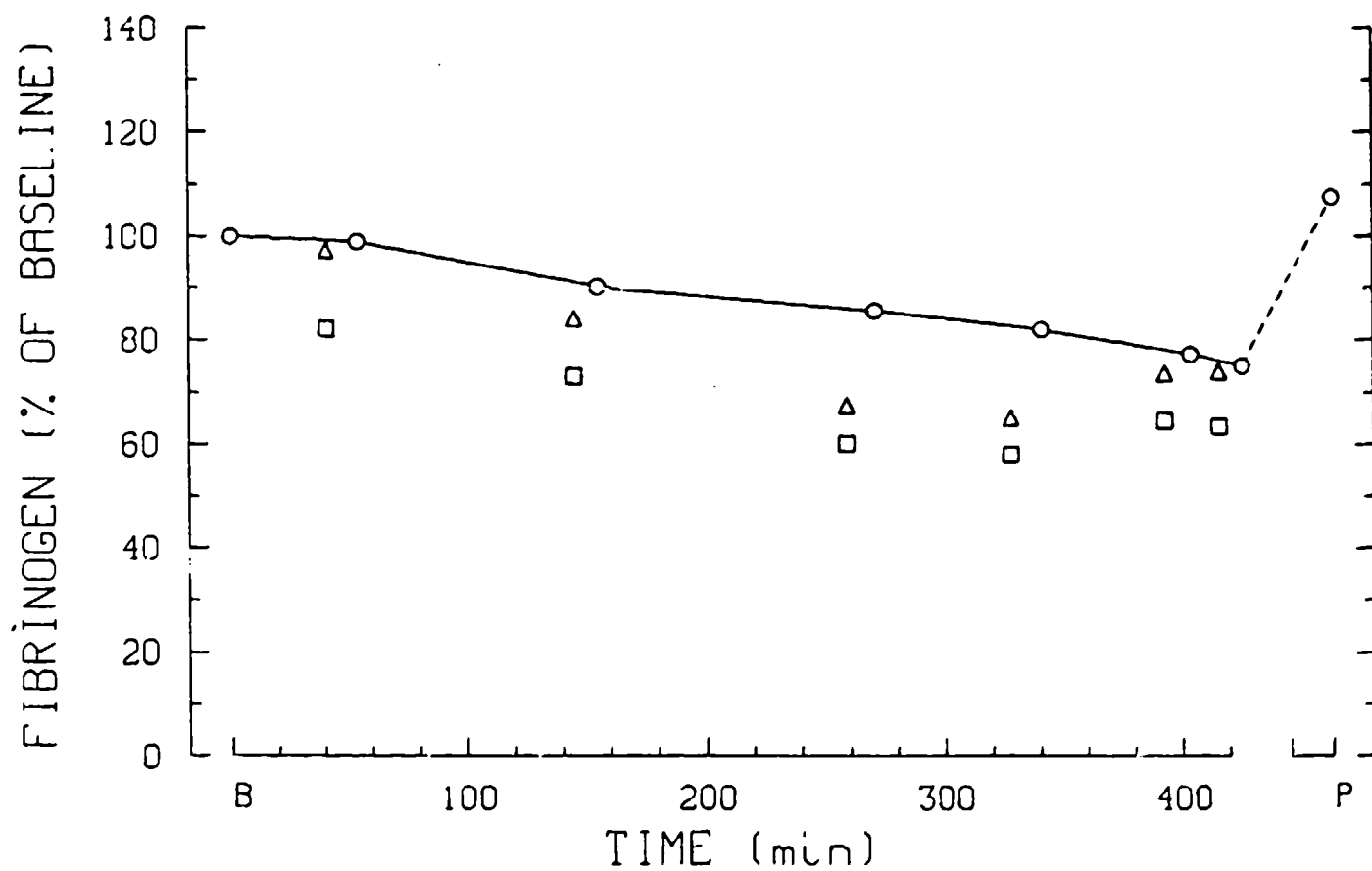
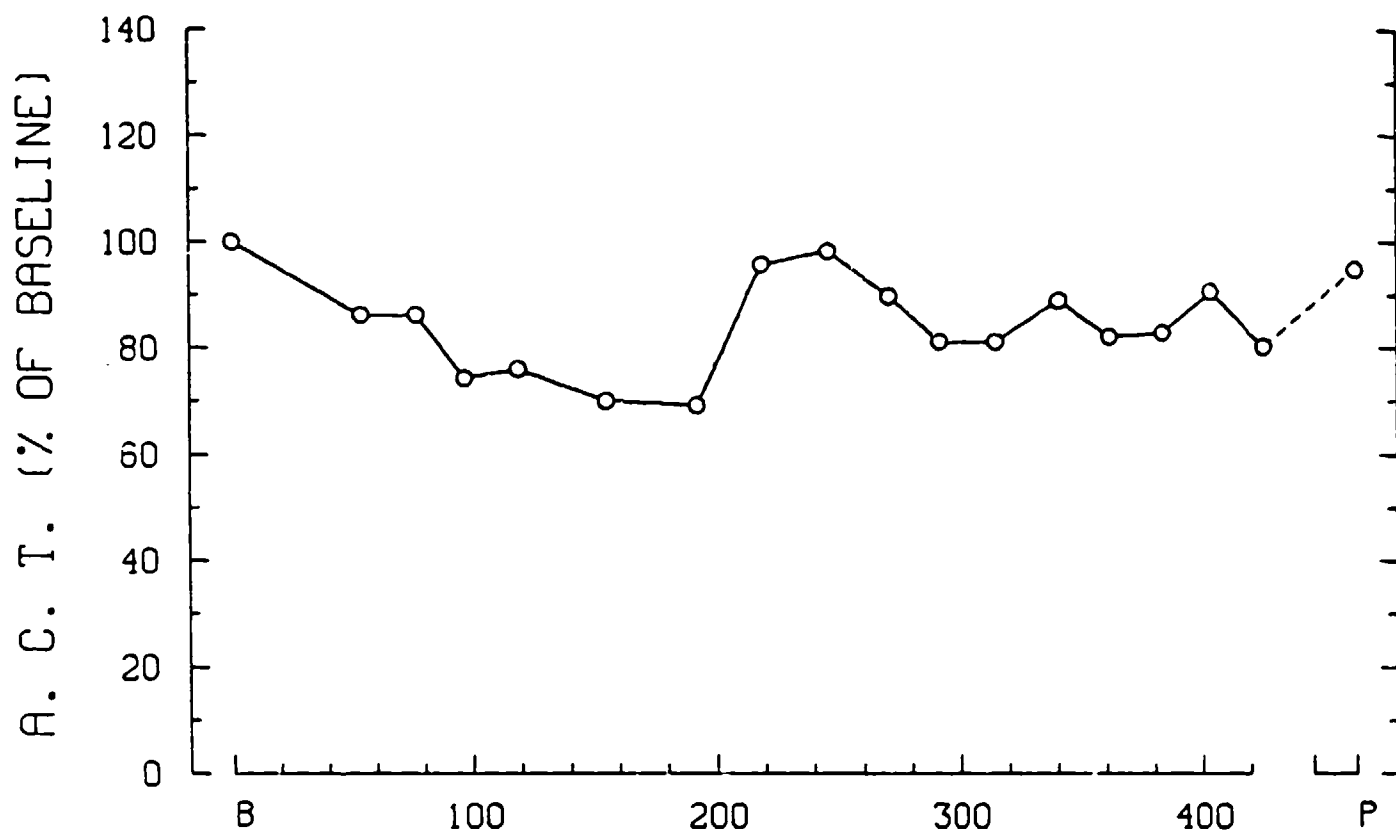


Figure A15: ATS Group Animal A9

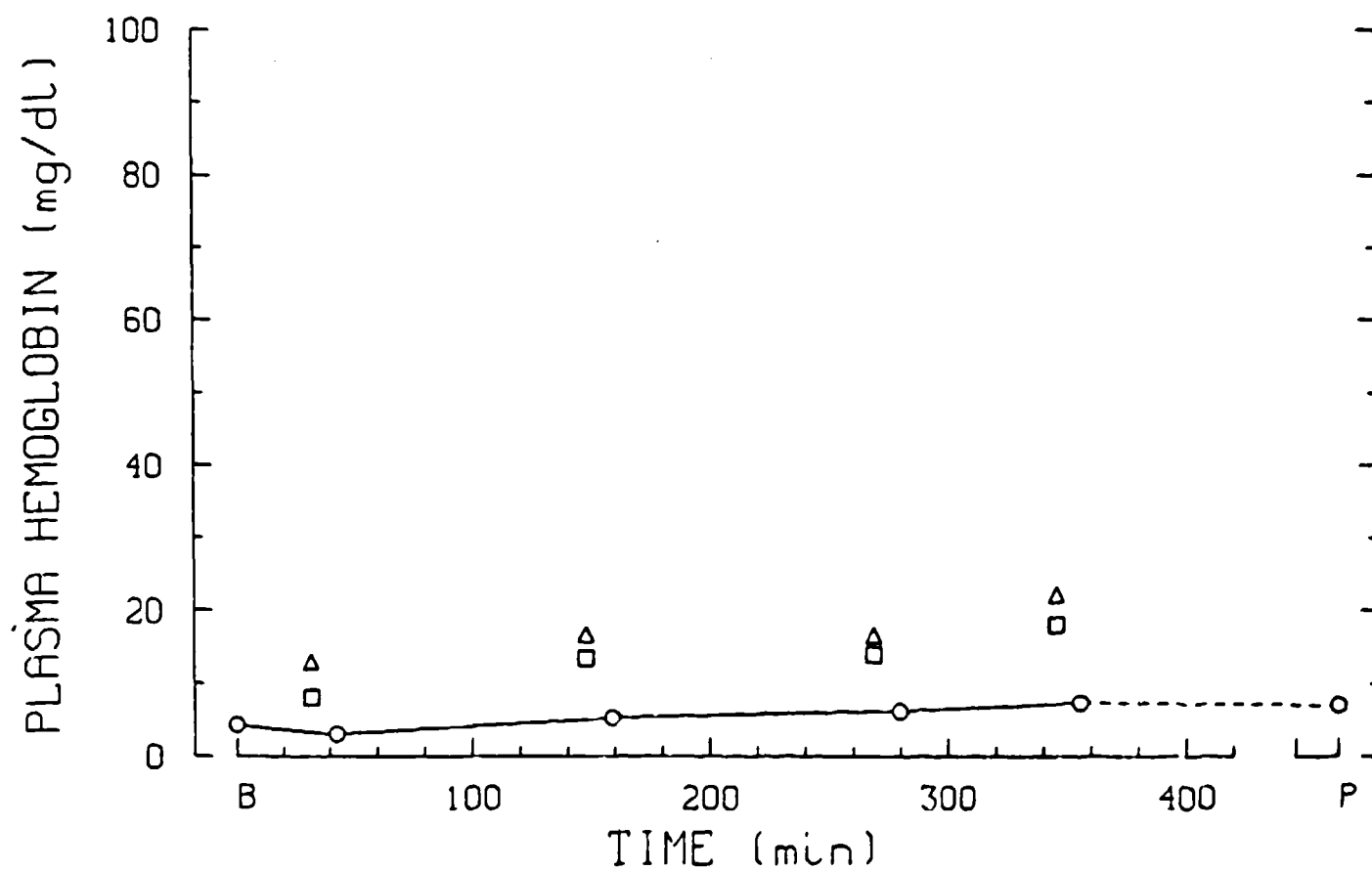
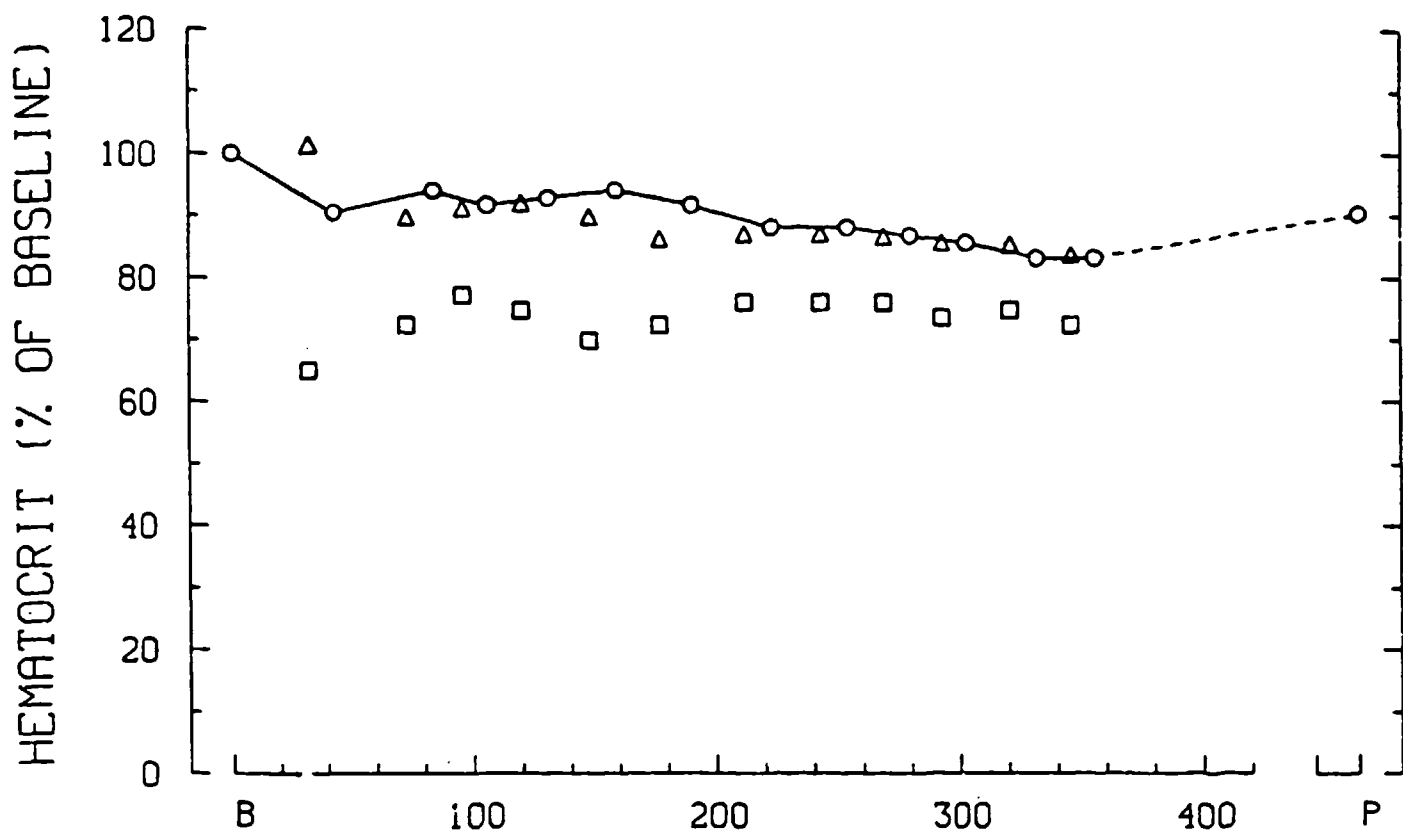


Figure A16: ATS Group Animal A10

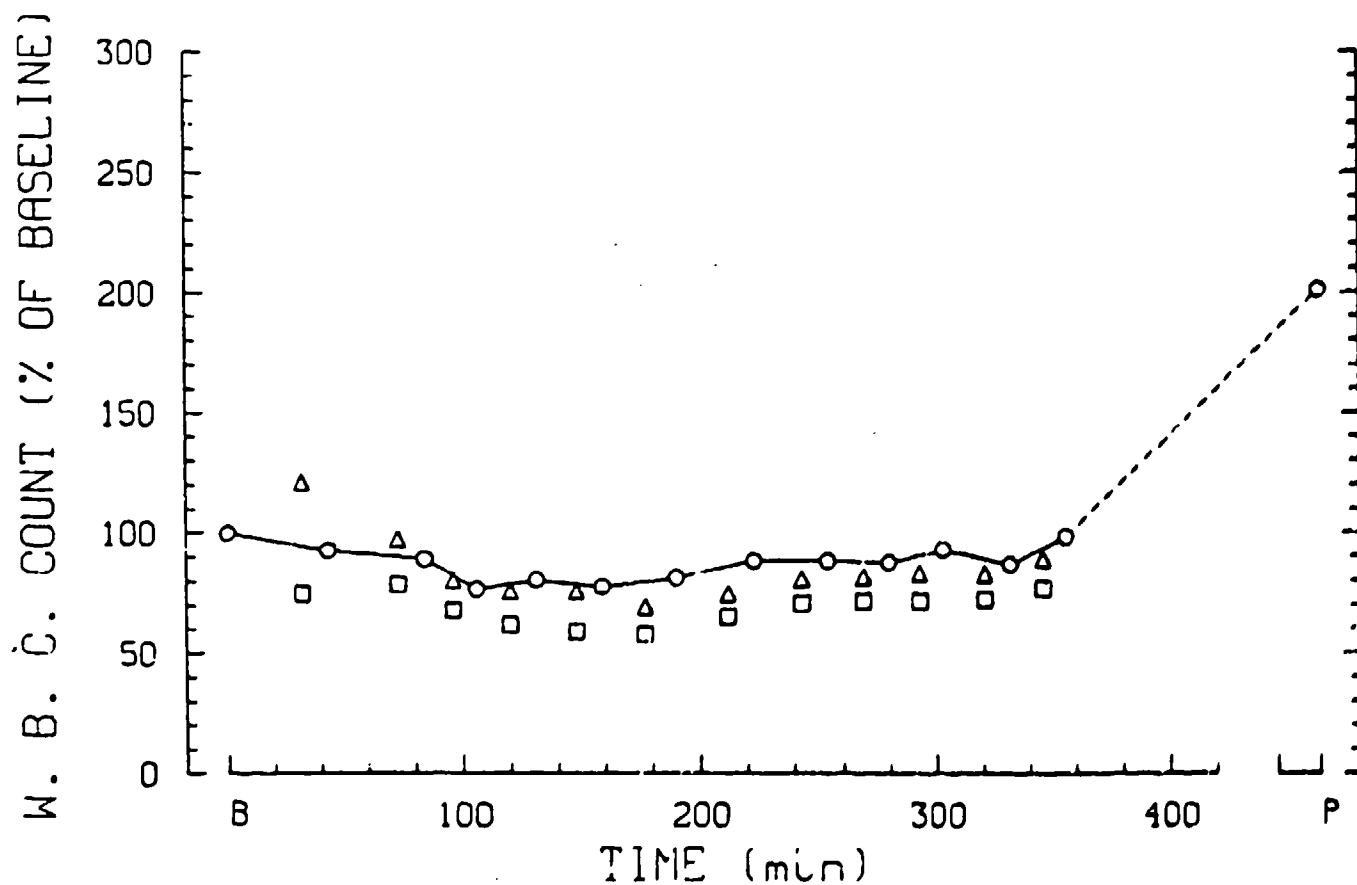
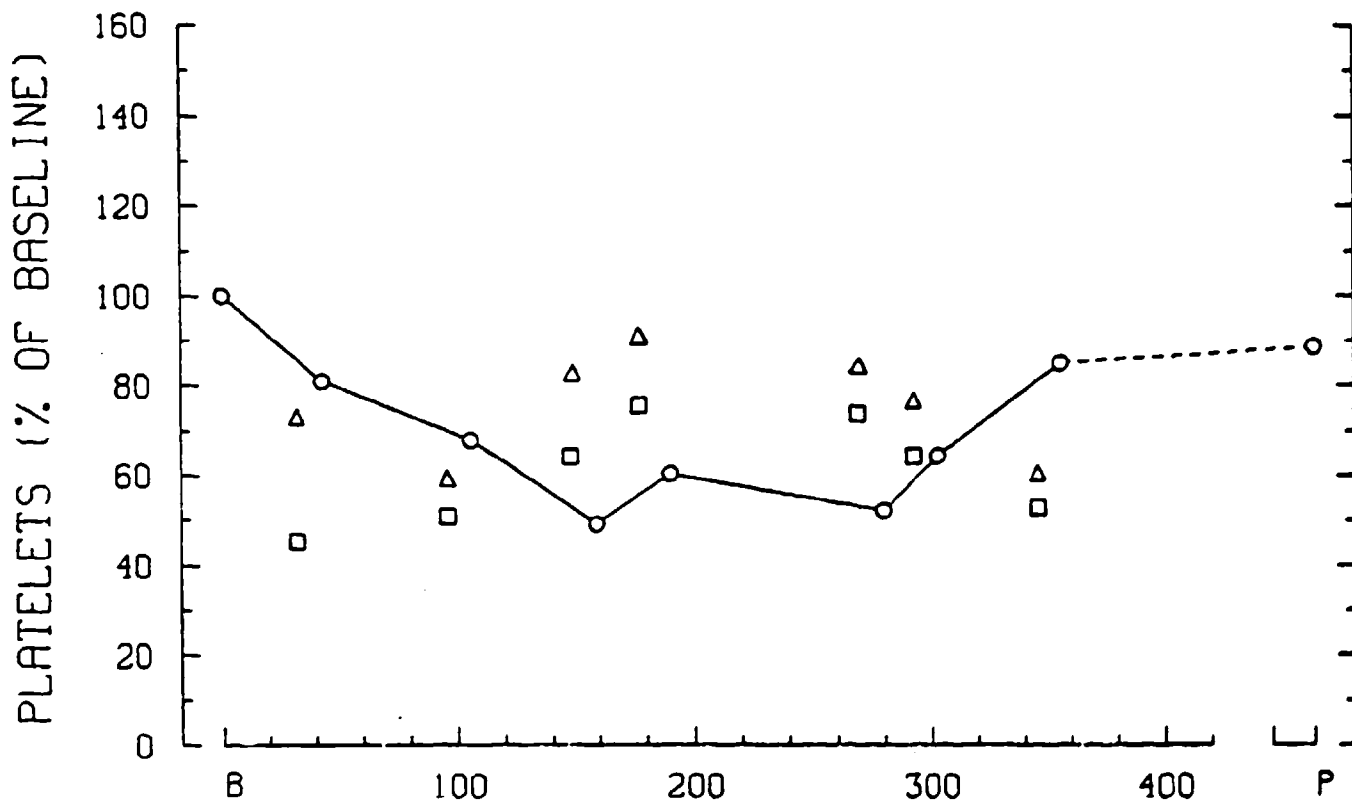


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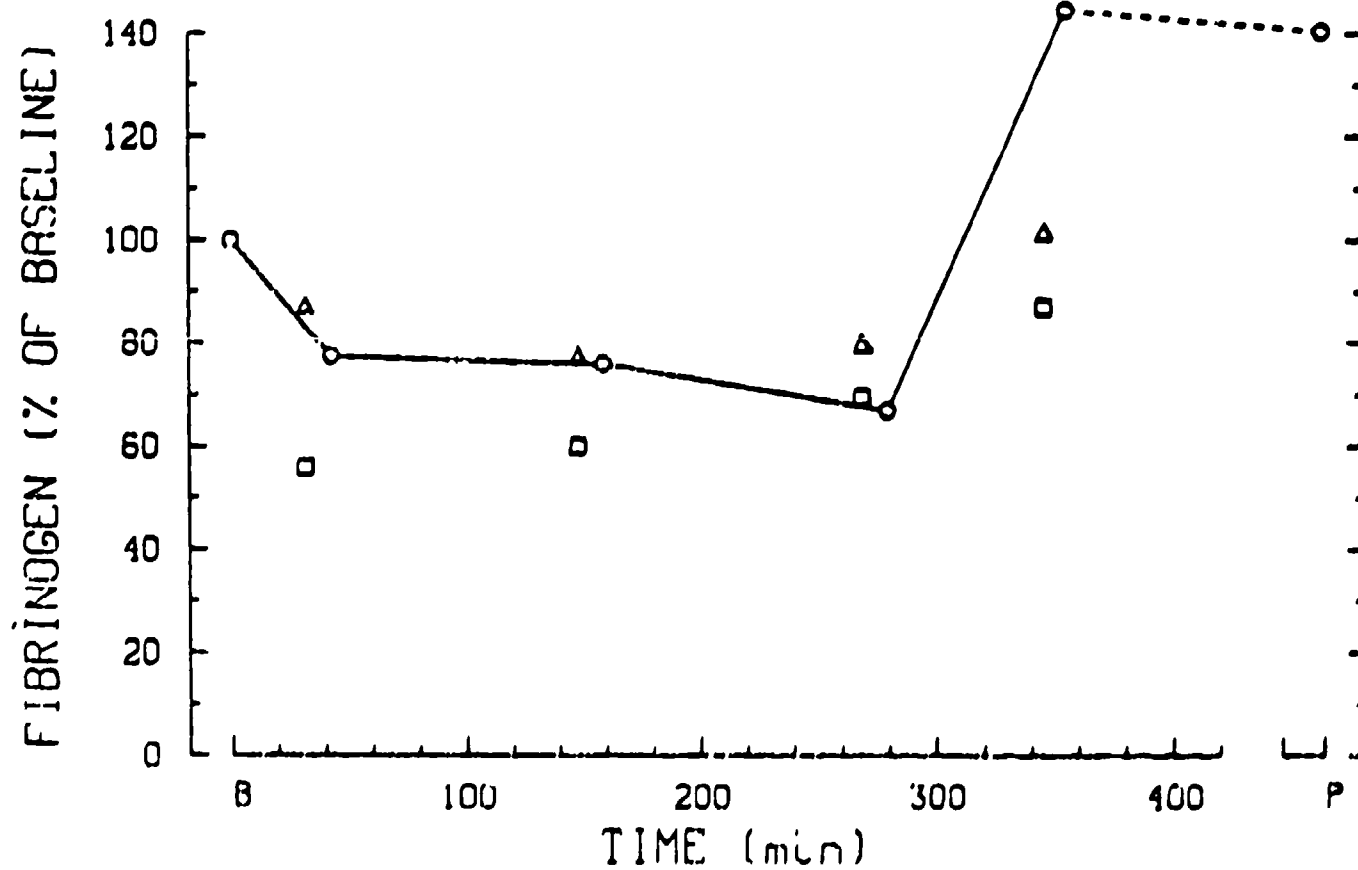
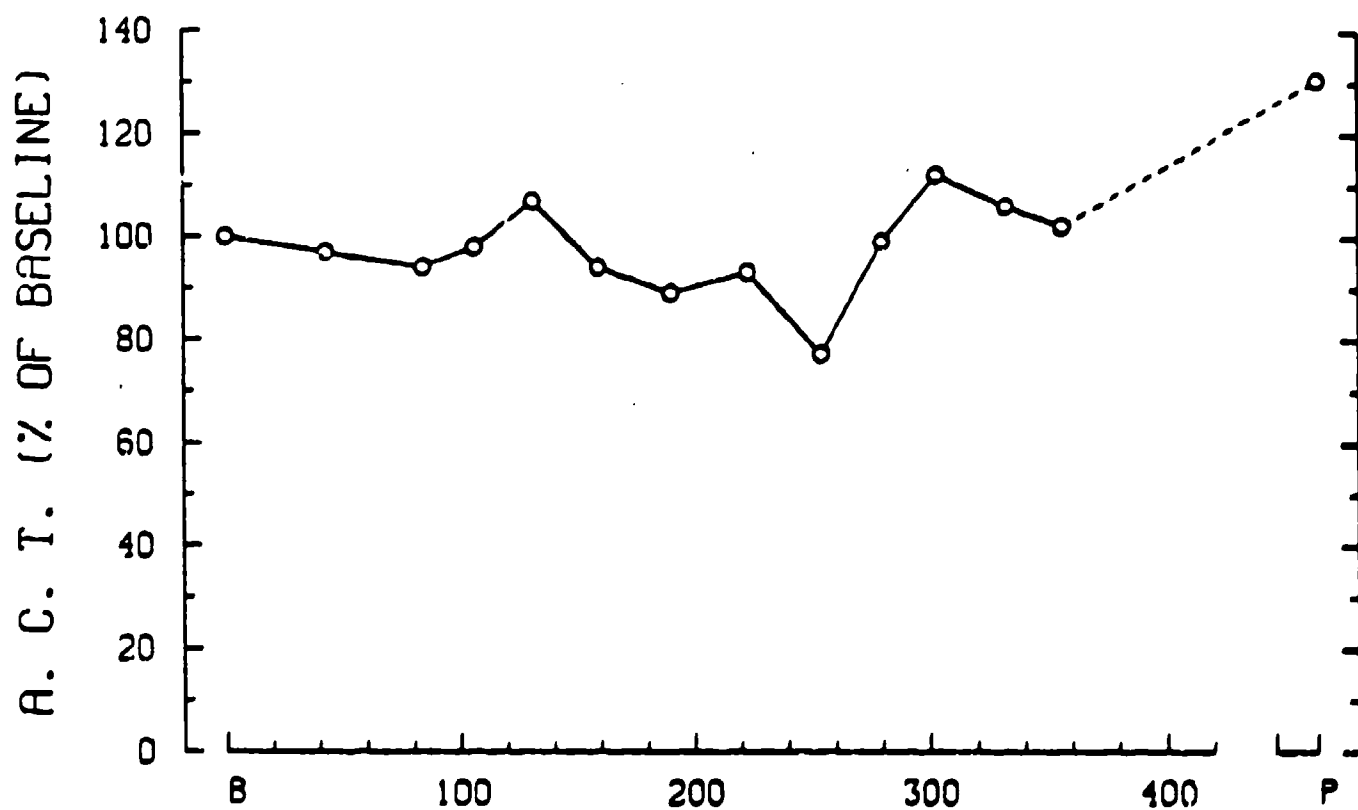


Figure A18: ATS Group Animal A10

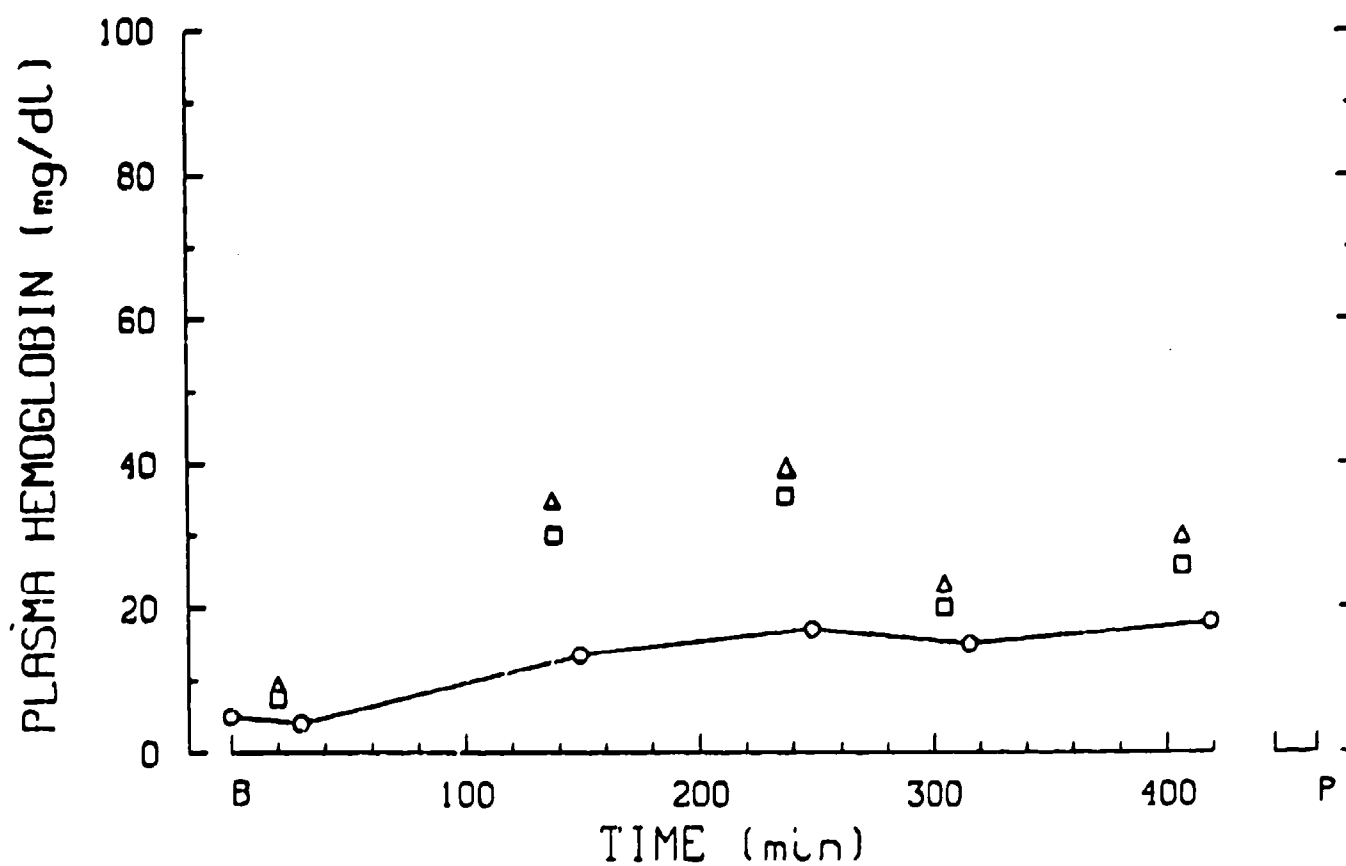
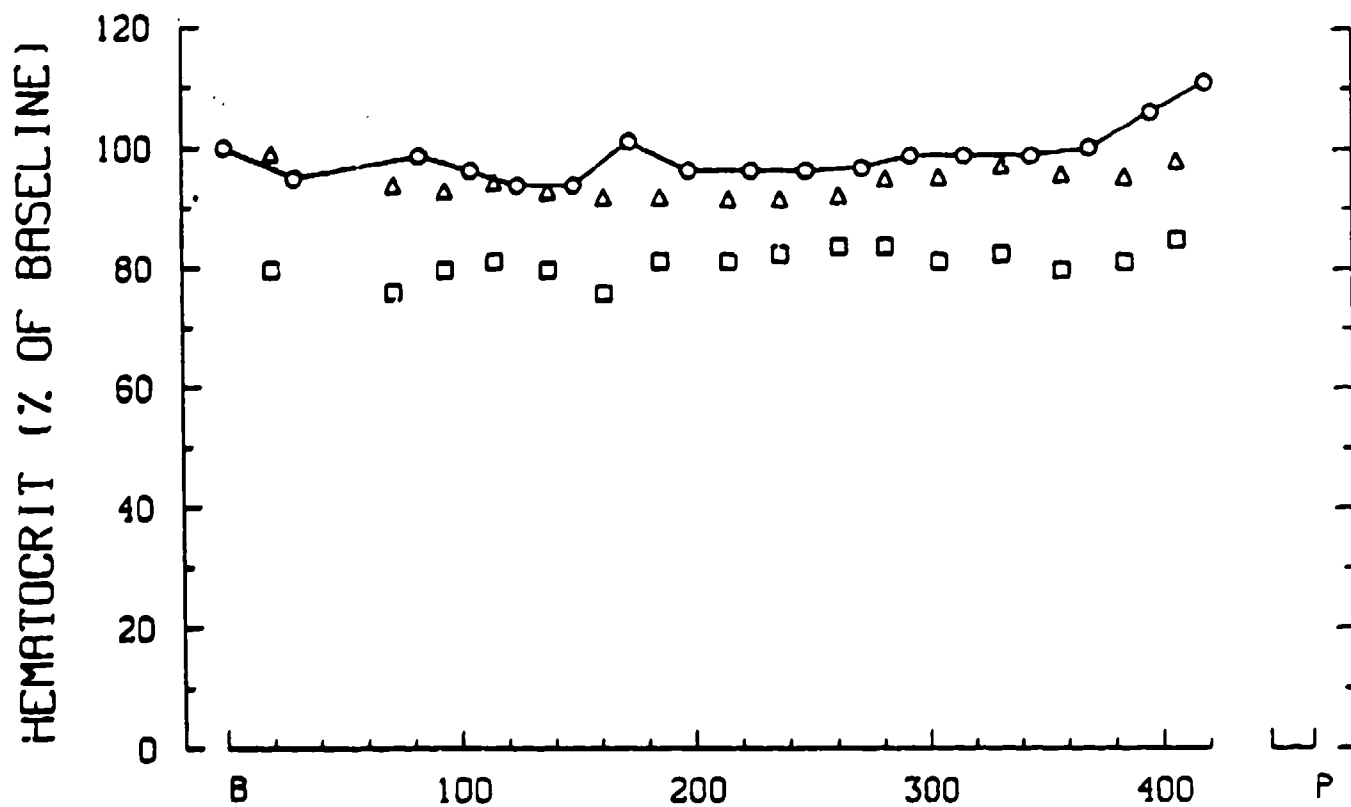


Figure A19: ATS Group Animal A11

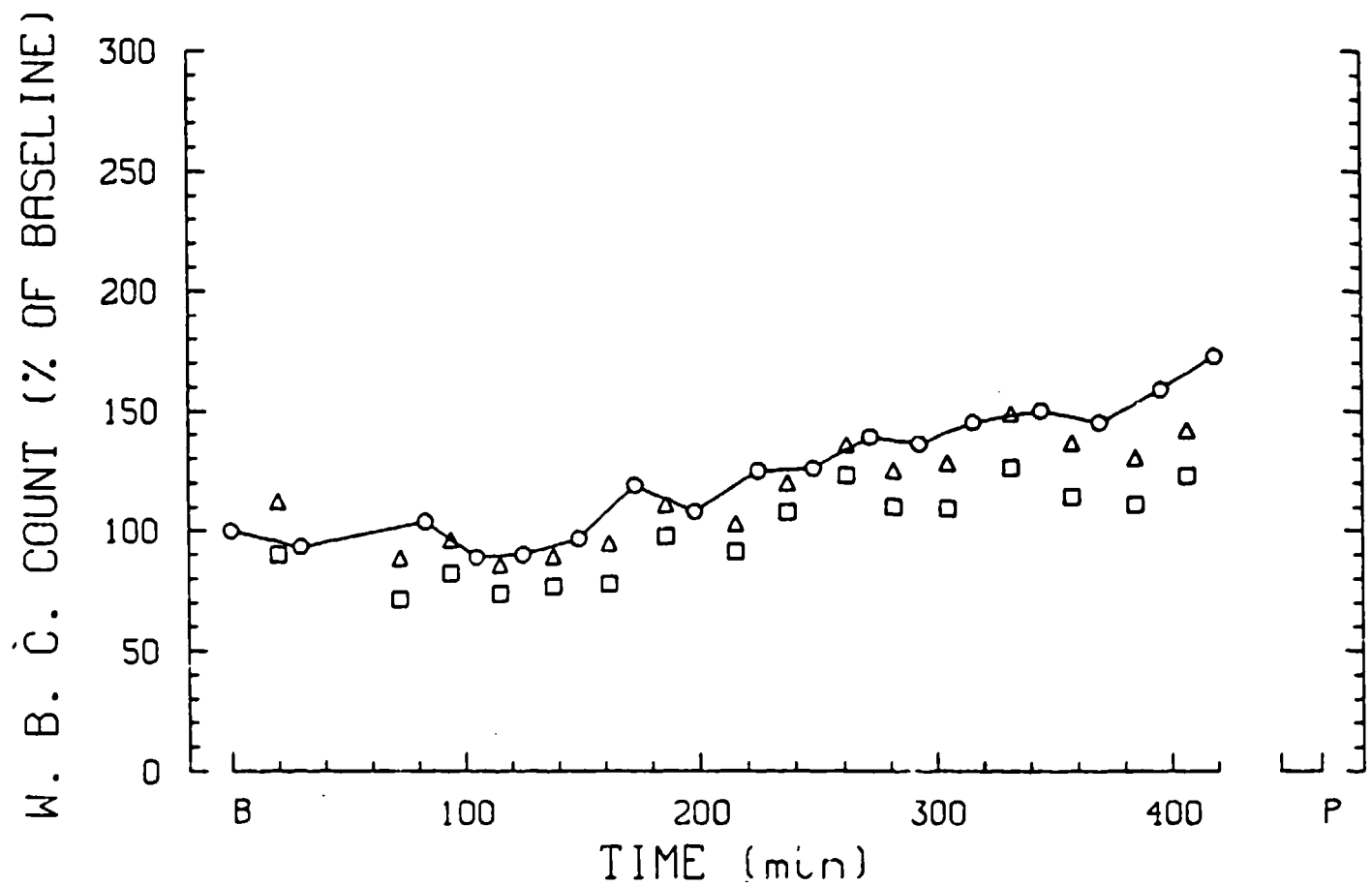
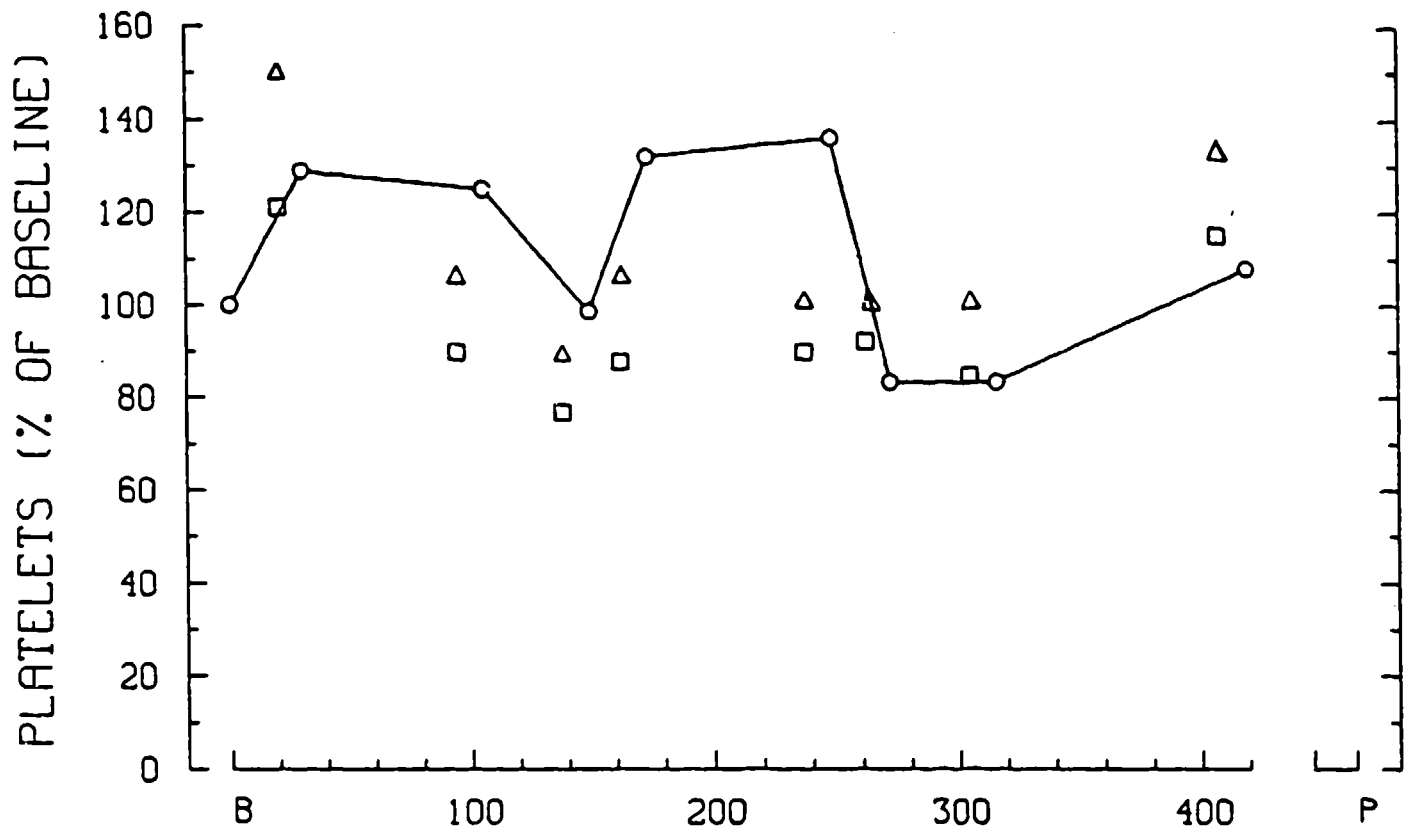


Figure A20: ATS Group Animal A11

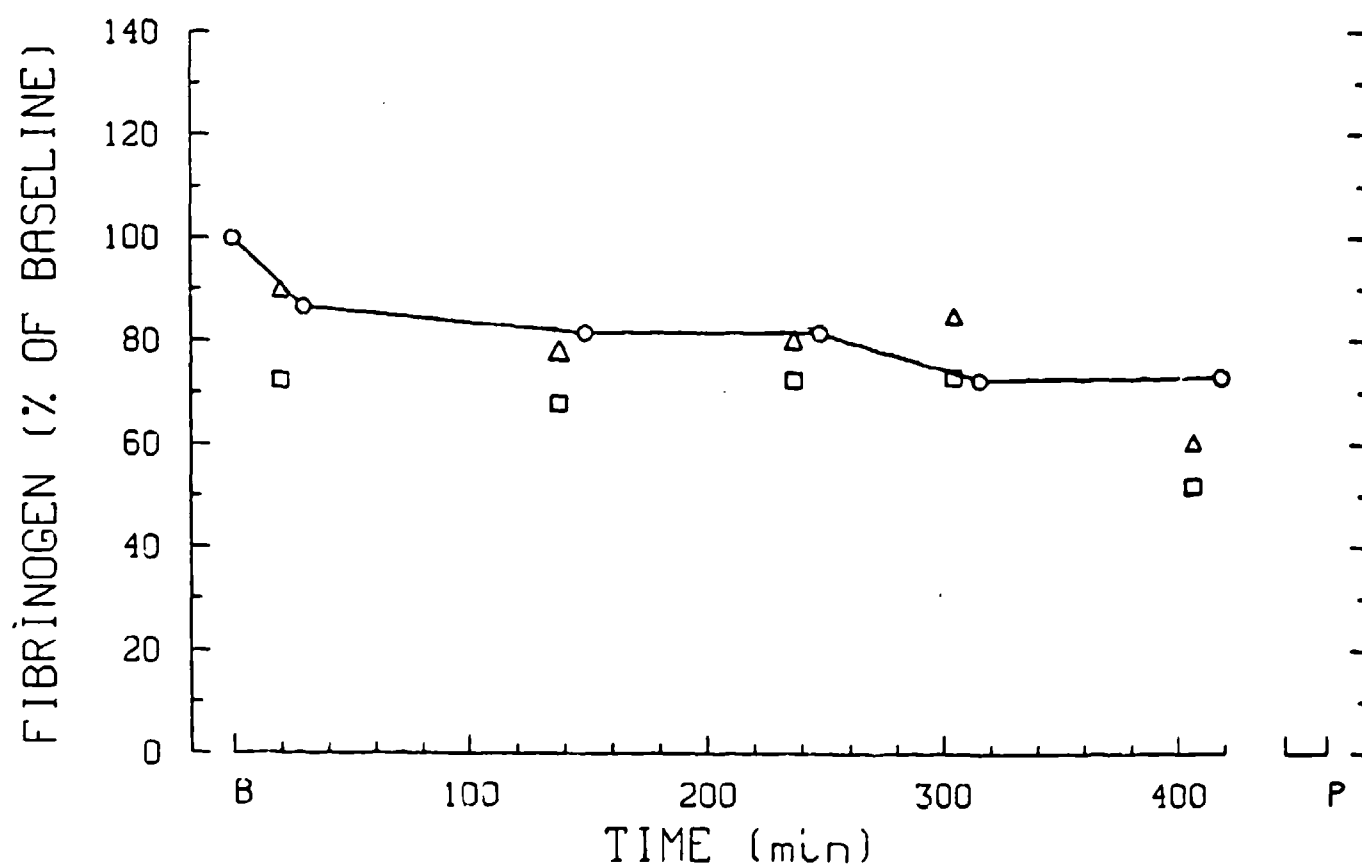
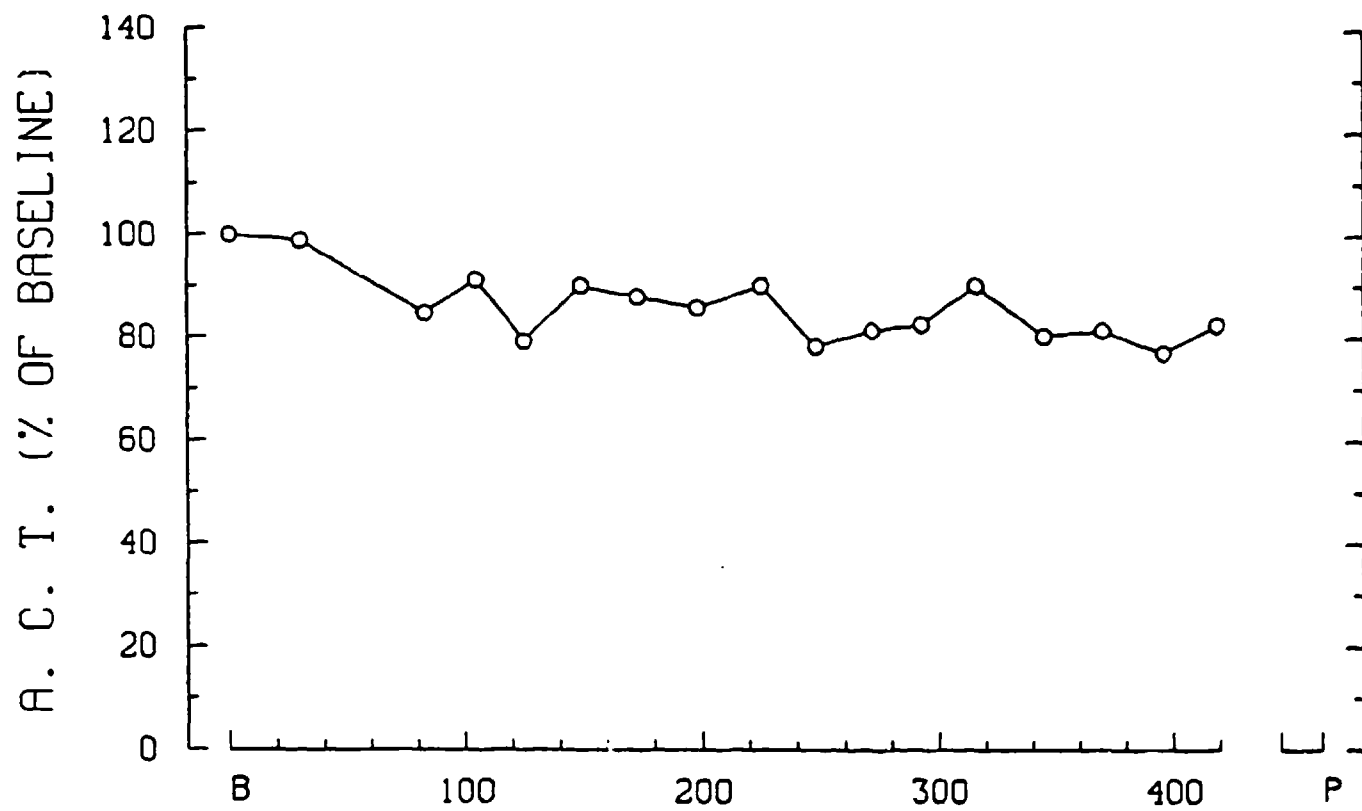


Figure A21: ATS Group Animal A11

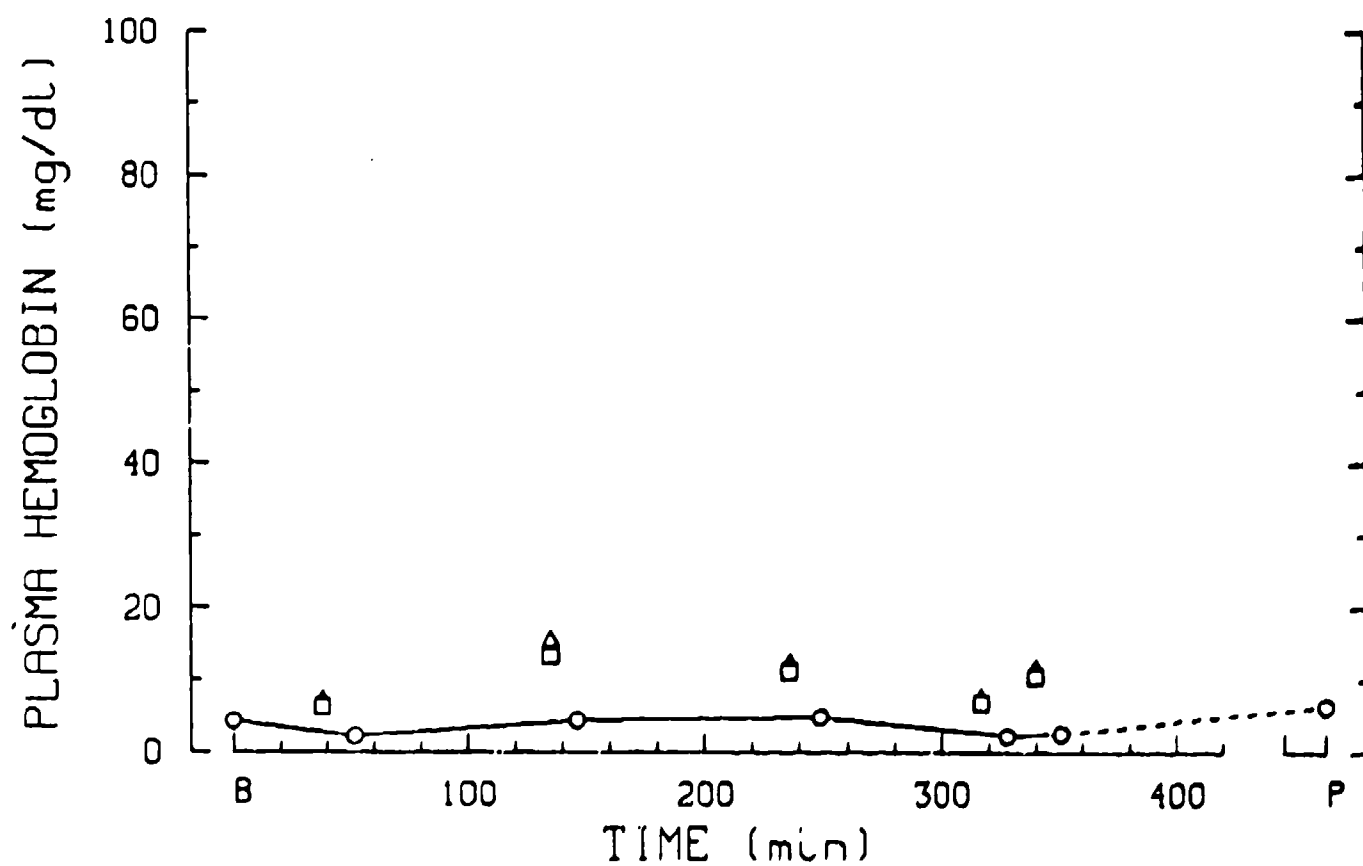
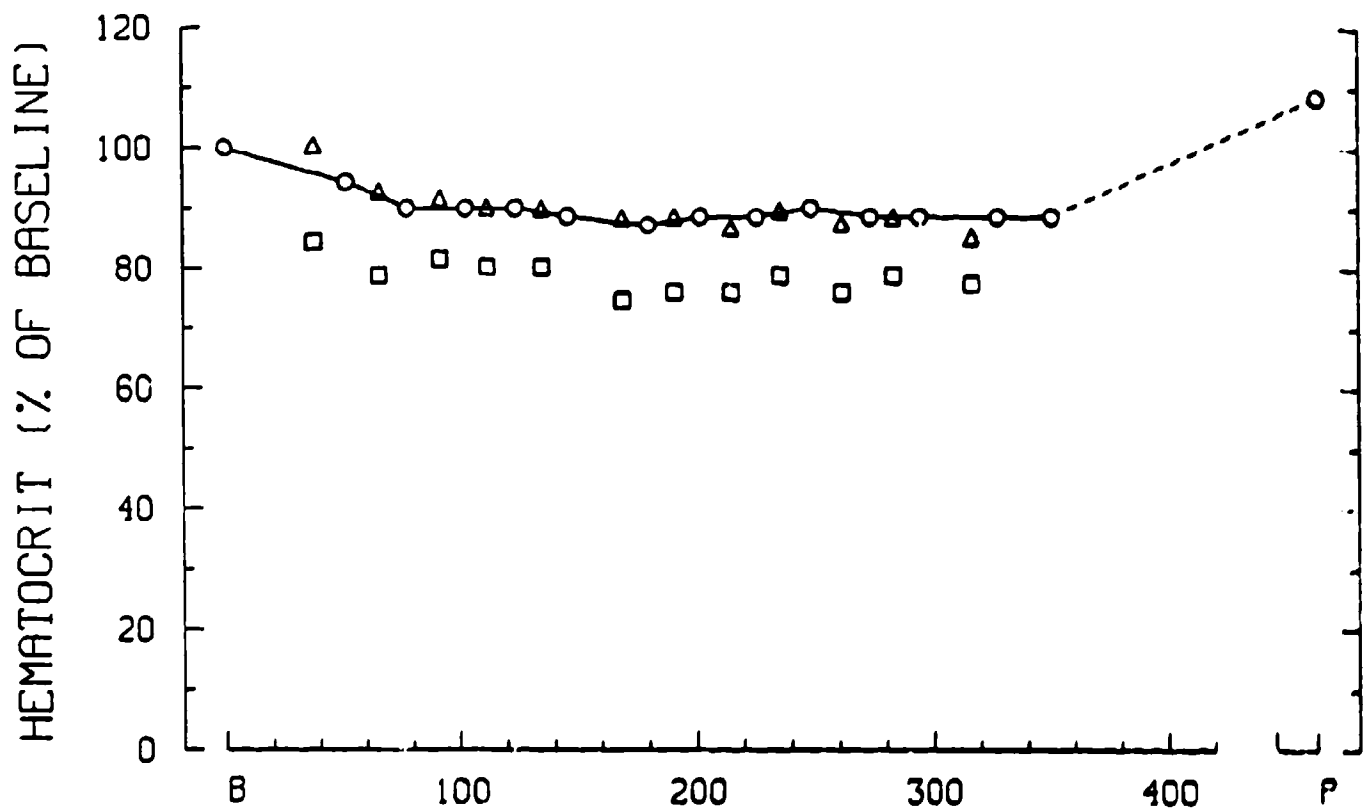


Figure A22: ATS Group Animal A12

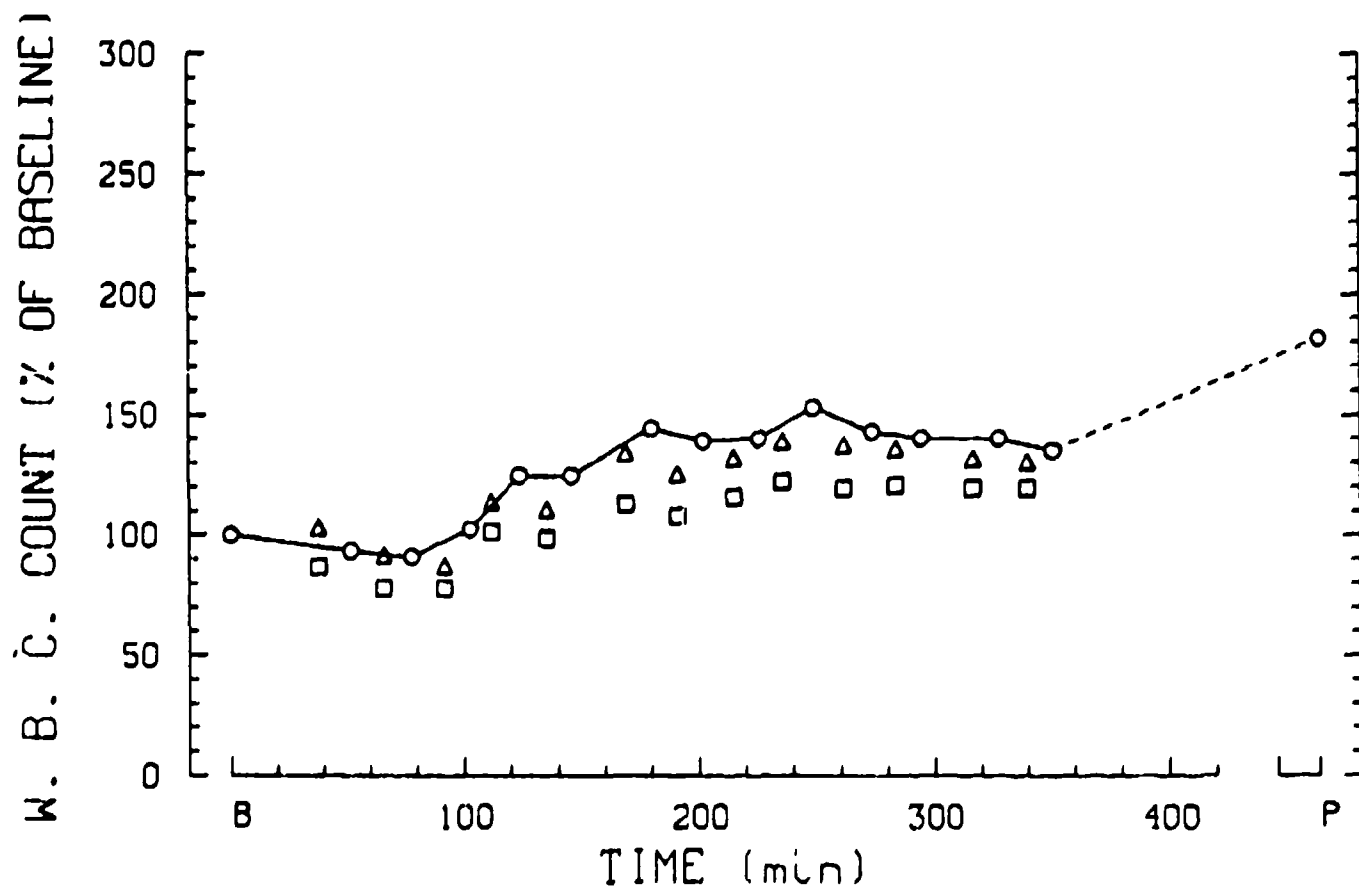
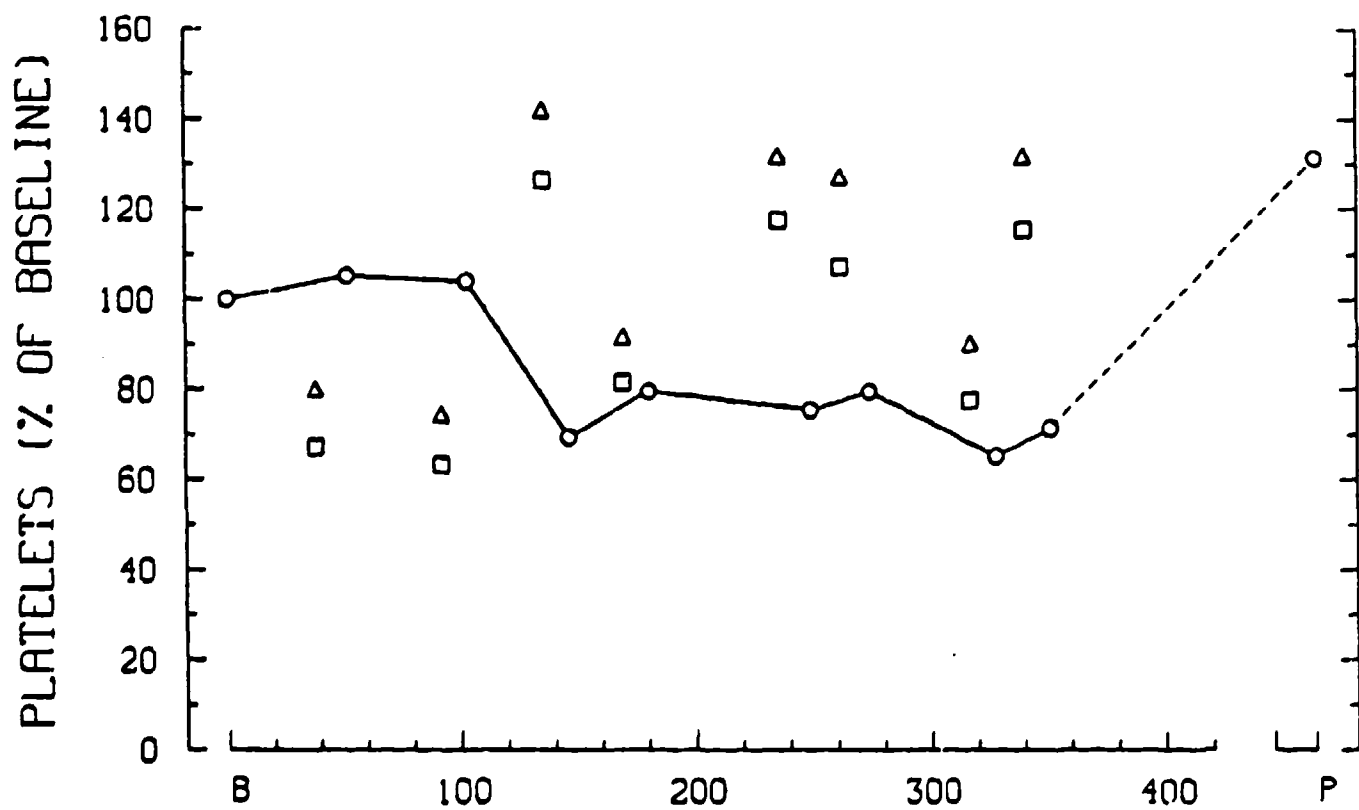


Figure A23: ATS Group Animal A12

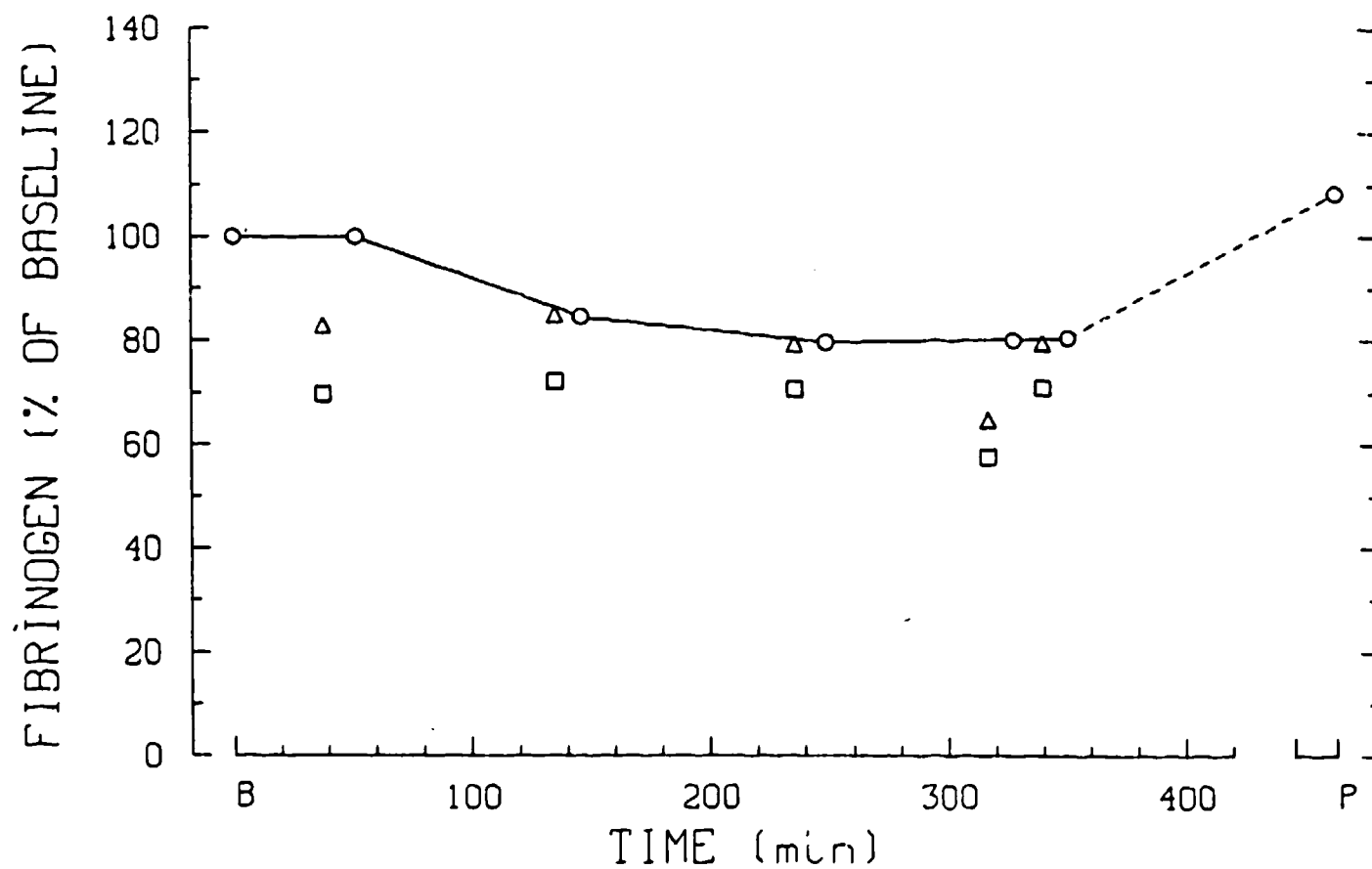
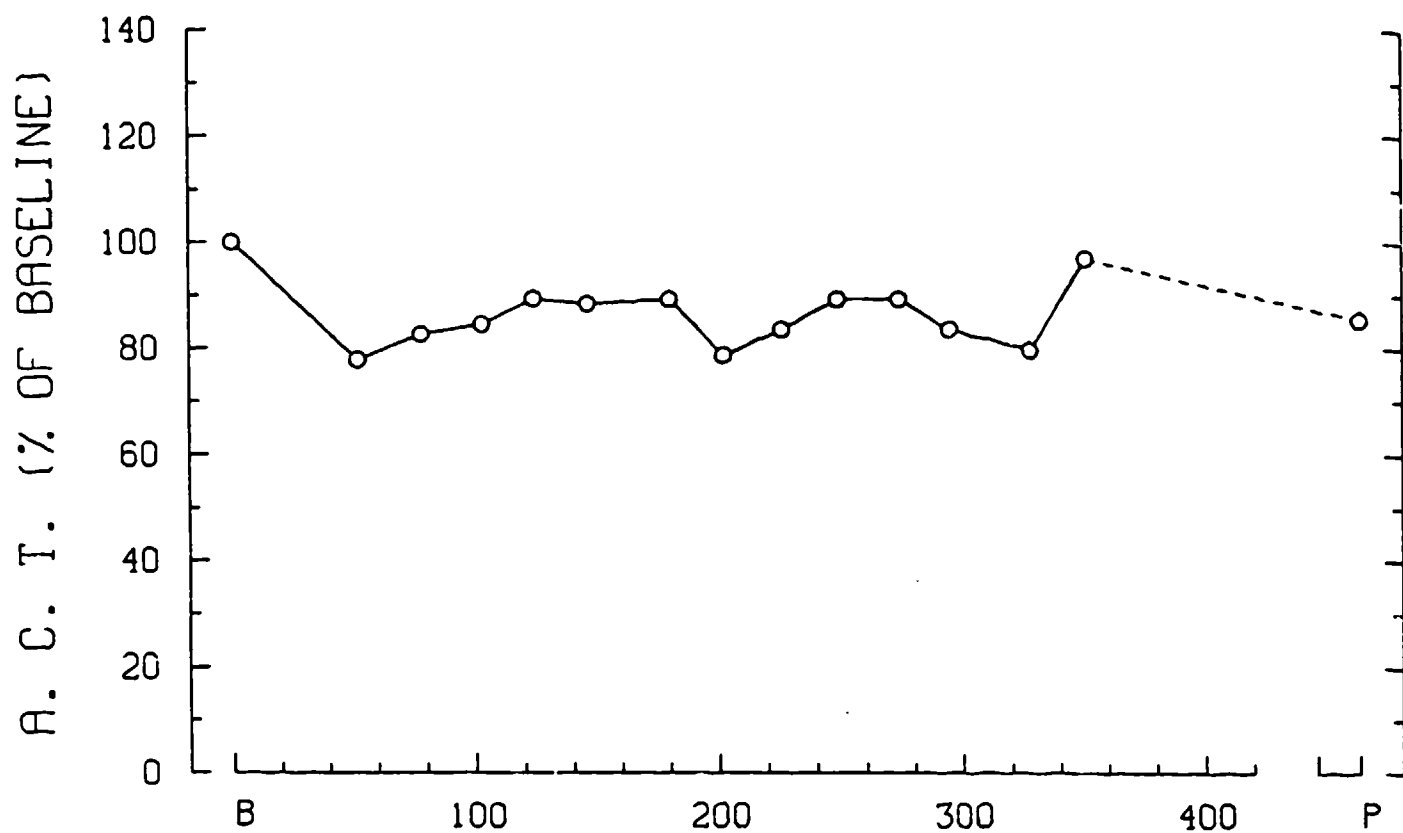


Figure A24: ATS Group Animal A12

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